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as conformationally restrained dipeptide mimics**

Dorsey, Gordon Owen

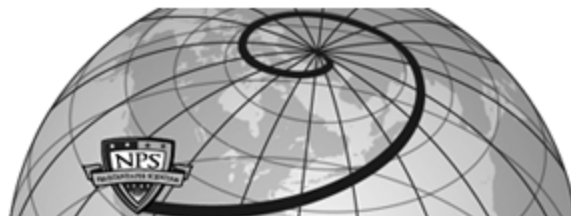
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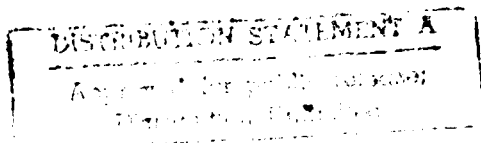
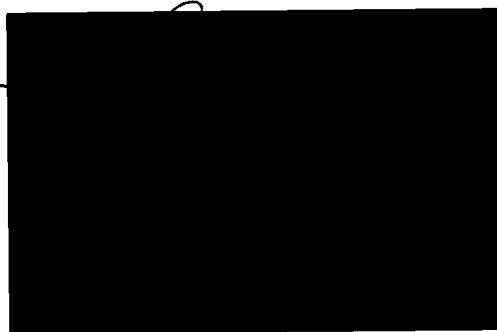


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DESIGN AND SYNTHESIS OF SUBSTITUTED CYCLOPROPANES
AS CONFORMATIONALLY RESTRAINED
DIPEPTIDE MIMICS

APPROVED BY:



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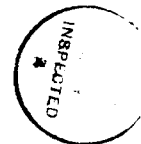
To Susan and

"life

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**DESIGN AND SYNTHESIS OF SUBSTITUTED CYCLOPROPANES
AS CONFORMATIONALLY RESTRAINED
DIPEPTIDE MIMICS**

by

GORDON OWEN DORSEY

THESIS

**Presented to the Faculty of the Graduate School of
The University of Texas at Austin
in Partial Fulfillment
of the Requirements
for the degree of**

MASTER OF ARTS

THE UNIVERSITY OF TEXAS AT AUSTIN

MAY 1992

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G. O. D.
April 1992

Table of Contents

CHAPTER 1.	CONFORMATIONALLY RESTRICTED PEPTIDE MIMICS AND HIV PROTEASE INHIBITION.	
1.1.	Introduction	1
1.2.	Conformational restriction and entropic binding advantage.....	2
1.3	Human Immunodeficiency Virus Protease	20
1.4	Bound Inhibitor Crystal Studies	31
CHAPTER 2.	RATIONAL DESIGN OF SUBSTITUTED CYCLOPROPANES AS PEPTIDE MIMICS.	
2.1.	Introduction	41
2.2.	Conformational Analysis of Known Inhibitors	42
2.3.	Analysis of Cyclopropanes Effect onConformation.....	44
2.4.	Cyclopropane as a ϕ Angle Restrictor	45
2.5.	Cyclopropanes as χ Angle Restrictors	46
2.6.	Conformationally Constrained Inhibitor Design	49
CHAPTER 3.	SYNTHESIS OF SUBSTITUTED CYCLOPROPANES AS PEPTIDE MIMICS.	
3.1.	Introduction	51
3.2.	Enantioselective Rh(II) Catalyzed Cyclopropanations.....	52
3.3.	Enantioselective Synthesis of Substituted Cyclopropanes	59
3.4.	Conclusions	75
CHAPTER 4.	EXPERIMENTAL PROCEDURES	78
REFERENCES	94
VITA	102

CHAPTER 1. CONFORMATIONALLY RESTRICTED PEPTIDE MIMICS AND HIV PROTEASE INHIBITION.

1.1. Introduction.

Molecular recognition plays a vital role in a wide variety of biochemical transformations. Of particular interest to chemists, biochemists, and biologists is the process by which enzymes recognize and bind substrates in the catalytic process. The relationship of peptide structure to properties and biological activity is the most important aspect of studies of molecular recognition. Enzyme binding studies are complicated because of the numerous variables in the binding process, which include the flexibility of substrates and inhibitors in solution, the paucity of enzyme structural information, and the dynamic nature of the enzyme/substrate complex structure.

Recent advances in X-ray crystallography and molecular modeling have allowed researchers to determine the coordinates of many bound inhibitor/enzyme complexes and analyze the bound conformation of inhibitors. The HIV-1 protease has been the subject of several recent X-ray crystallographic studies, so the general topography of bound HIV-1 protease inhibitors is well established. In addition, numerous HIV protease inhibitor and substrate binding studies have established the enzyme's ligand preferences at important binding subsites.

Conformationally restricted pseudopeptide substrates and inhibitors have an entropic binding advantage over their more flexible, unconstrained analogues and have been found to enhance binding in several studies. Rationally designed, conformationally restricted peptide mimics that fix backbone and side chain

orientation in the "bound" geometry enhance binding and can be used to probe the enzyme binding site by varying the properties of the restricted ligands. 1,2,3-Trisubstituted cyclopropanes are among the most effective conformationally restricted dipeptide mimics. They fix both the amino acid side chain and backbone orientations and can be efficiently synthesized via enantioselective transition metal catalyzed intramolecular cyclization of allyl diazoacetates.

Our goal in this research project was to design a series of substituted cyclopropanes as peptide mimics, develop enantioselective synthetic pathways to these compounds, and investigate methods of coupling di- and mono-peptide mimics into effective HIV protease inhibitors that can be used to evaluate the effect of ϕ (ϕ) and χ (χ) angle restrictions on inhibitor binding .

1.2. Conformational restriction and entropic binding advantage.

Small peptides are quite flexible in solution. Conformational interconversions not requiring peptide bond rotations may occur at milli-second or faster time scales, and peptide bond rotations occur on the time scale of seconds.¹ Upon binding to an enzyme active site, the section of the substrate peptide that is bound to the host enzyme has a relatively rigid three-dimensional (3-D) structure. Conformational restrictions that mimic the bound 3-D structure of a peptide offer an entropic binding advantage per the four principles of conformational restriction in binding that are set forth below.

- (1) Binding involves loss of entropy for the ligand, the enzyme and the system
- (2) Binding energies pay for entropic advantage

(3) You must pay for loss of entropy only once

(4) Entropy loss "bought" in synthesis gives binding advantage

In considering the advantages of conformational constraint, it is important to realize that the concept of conformational constraint is a double-edged sword in that restrictions which do not closely mimic the bound 3-D structure of the peptide of interest can negatively affect the binding process. Although some variations from optimal geometry may be compensated for by an induced fit between the peptide mimic and the enzyme, significant deviation may prevent binding or reduce binding efficiency.

1.2.1. Natural amino acids and conformational restraint.

Peptide conformation and topography are described by phi (ϕ), and psi (ψ), and chi (χ) angles as illustrated in Figure 1. Phi (ϕ) represents the amount of rotation at the bond between an amino acid residue's nitrogen and α -carbon and psi (ψ) represents the amount of rotation at the bond between the α -carbon and carbonyl carbon atoms. Together, ϕ and χ angles for each residue in the peptide chain completely define main chain conformation since amide bonds are considered to be rigid and planar. In a fully extended polypeptide chain $\psi = \phi = 180^\circ$ and in the sterically favored extended β -sheet backbone configuration residue angles of $\psi = +135^\circ$ and $\phi = -135^\circ$ are common. Chi 1 (χ^1) represents the amount of rotation at the bond between the α -carbon and β -carbon of a residue and defines the orientation of the residue's sidechain. Three common examples of χ^1 orientations for β -substituted amino acids are shown in Figure 1. Gauche (+) ($\chi^1 = 60^\circ$), gauche (-) ($\chi^1 = -60^\circ$) and anti ($\chi^1 = 180^\circ$) are commonly used in discussion of side chain

orientations and their abbreviations of g^+ , g^- , and *anti* will be used in the discussion below.²

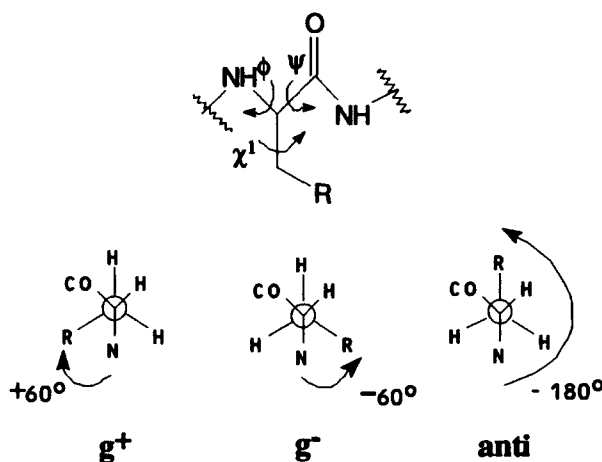


Figure 1

Proline (Pro), valine (Val) and isoleucine (Ile) all have structural features that affect the conformation of peptides into which they are incorporated. Proline's cyclic structure restricts ϕ and χ angles causing it to have a profound influence on the conformations of peptide segments and protein folding.³ Proline is strongly favoured in position $i+1$ of β -turns and is of interest in this study because it occupies the PI' site in three of the eight substrates for the HIV-1 protease discussed below.¹

Val and Ile are both β -substituted by a methyl group, which in conjunction with their other β -ethyl or methyl substituents, imparts a preferential χ angle to the residue. Figure 2 details the low-energy side chain conformation for Val and Ile about the $C_{\alpha}-C_{\beta}$ bond. Steric considerations indicate that the conformation B would be preferred. This preference should impart enough local conformational stability to affect molecular recognition. Both these β -substituted amino acids are

important residues in the HIV inhibitors used as geometrical templates in this study and their "bound" conformations will be analyzed in detail below.

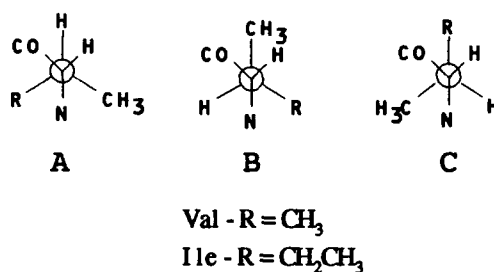


Figure 2

1.2.2. Conformational constraint in peptide mimics.

Two levels of conformational constraint have been utilized to design peptide and protein ligands with specific physical, chemical, and biological properties. Global restraints in the form of β -turn and α -helix templates impart specific secondary backbone structures to peptides.⁴ Local conformational restraints bias or constrain side chain moieties of a peptide or pseudopeptide residue to a particular side chain conformation χ -angle without affecting the overall backbone configuration. Seven general methods of inducing local constraint have been reviewed by Hruby and are listed below with the expected effects on conformation.⁵

General Methods of Inducing Local Constraints in Peptides

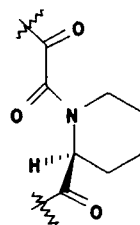
<u>Method</u>	<u>Constraints</u>
(1) Backbone N - alkylation	ϕ, ψ, χ^1
(2) Backbone C - alkylation	ϕ, ψ
(3) D-amino acid or Proline Substitution	ϕ, ψ, χ^1
(4) Bulky Side Chain Groups	χ, ψ
(5) Amide Bond Surrogates trans (double bond) cis (tetrazole)	ψ
(6) Cyclic Amino Acids side chain to backbone	ϕ, ψ, χ
(7) β -alkylated, β -hydroxylated amino acids	χ^1

Backbone N- and C α -alkylation and the addition of bulky side chain groups induce local constraints on peptide conformation by limiting the number of sterically favorable conformations about the C α to N and C α to carbonyl carbon bonds. N-alkylation favors *cis* configurations at the affected amide bond and C α -alkylation tends to initiate turns in peptide backbone chain orientation. The extended β -sheet (or β -strand) configuration in a peptide generally represents the most sterically favored conformation with all *trans* orientation at amide bonds and no turns. Backbone N- and C α -alkylation, and amide bond surrogates disrupt the extended β -sheet conformation needed to mimic the geometry observed in bound inhibitors of the HIV protease and bulky side chain groups are not expected to fit in the enzyme's relatively specific and compact binding sites, so N-alkylation, C-alkylation, amide bond surrogates, and bulky side groups were not considered as

potential methods of restricting conformation when designing potential constraints to probe the HIV protease. Proline or proline analogue substitution, cyclic amino acids and pseudo-peptides and β -substituted amino acids were considered as potential constraints and are reviewed below.

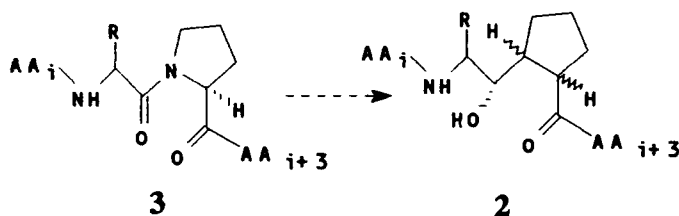
1.2.3. Proline and proline analogues as conformational constraints.

Schreiber asserts that the N-acyl substituted pyridine 1 serves as a "twisted" proline mimic in substrate specificity studies for the human rotamase FKBP. This "proline analogue" was used to orient adjacent ligands in rapamycin and a synthetic analogue FK506 into the S1 binding site of the enzyme. Molecular modeling studies of the pyridine based inhibitors indicated that the enzyme binding site would accommodate branched hydrophobic residues better than other types of residues and this was found to be the case in the related substrate specificity study.⁶ The residues studied were adjacent to, and not directly constrained by, the mimic and the cyclic mimic is still relatively flexible. It is difficult to attribute a preferred orientation to the molecule with enough confidence to predict the twisted geometry Shreiber asserts as a major factor in binding and more recent work involving bound FK506/X-ray crystal structures has shown this hypothesis to be incorrect. The peptidyl-prolyl amide bond was bound in a planar configuration.⁷



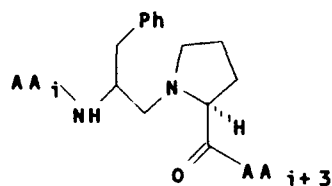
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Hydroxyalkyl isosteres like **2**, which mimic proline at the P1' subsite of potential protease inhibitors, have been synthesized stereoselectively.⁸ These compounds are designed to mimic both the sp^3 geometry of transition state scissile carbonyl carbon and the backbone orientation of the Xxx-Pro scissile amide bond of compounds like **3** below.



3

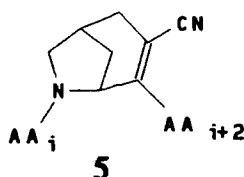
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4

Substrate-based, reduced amide inhibitors similar to compound **4** have been used to develop effective inhibitors of renin.⁹ The tetrahedral geometry of the reduced carbon mimics the accepted transition state geometry at the carbonyl carbon. The proline nitrogen mimics the basic nitrogen of the amide cleavage

product, and the proline ring provides conformational restraint. Reduced amide proline mimics have been incorporated into the P1' site of HIV-1 protease inhibitors with some success but the best inhibitors (Inhibition constants (K_i) = 19 μ M) are not as effective at the inhibitor P1' position as other P1-P1' transition state mimics discussed below (K_i < 10 nM are considered good).¹⁰

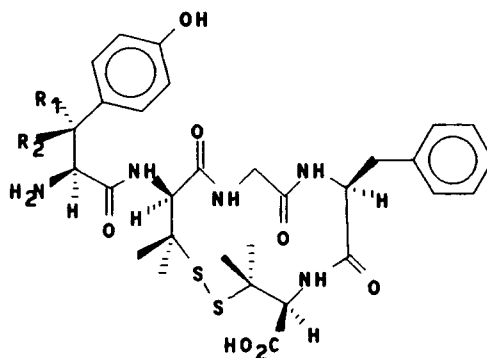


Kemp and Carter constructed bicyclic β -enaminonitrile **5** as γ -turn templates and conformationally restricted analogues of polypeptides from L-hydroxyproline. The bicyclic structures were not only more rigid than monocyclic β -enaminonitriles, which are also potential conformational restraints, but they are more resistant to epimerization because the bridgehead carbon cannot readily achieve the sp^2 geometry necessary for epimerization per Bredt's rule.¹¹ Although conformational analysis indicates that these mimics may be useful as conformational restraints, there are no studies of their effectiveness in pseudopeptides.

Proline and the proline mimics discussed above initiate turns and position side chains of adjacent residues indirectly. They do not, however, readily accommodate an extended β -sheet configuration and, there are no examples, to date, where substituted prolines or pseudo-prolines were used to directly position substituents in a binding site.

1.2.4. β -alkylated amino acids as conformational restraints.

Enantiomers of β -methylated D- and L-phenylalanine and tyrosine were used to modify systematically the topography of enkephalin analogue [D-Pen2,D-Pen5] enkephalin (DPDPE) (**6**), which is an effective δ opioid receptor selective agonist.¹² By methylating at the pro-S position (R_2) or the pro-R position (R_1), sidechain χ^1 angle preferences could be controlled by limiting the number of sterically preferred conformations about the $C\alpha$ to $C\beta$ bond. NMR studies of the conformation of resulting compounds indicated that the backbone conformation of this compound was not changed by the modification. However, the β -alkylated aromatic side chains did show a definite conformational preference (g^- for $R_2 = \text{Me}$ and g^+ for $R_1 = \text{Me}$) that defined a new topography for the pseudopeptide and significantly modulated its potency.¹³



(DPDPE) $R_1, R_2 = H$

6

Hruby carried the β -alkylation concept one step further, and incorporated β -methyl substituted Phe and Tyr amino acids into somatostatin analogues. He discovered that β -alkylation improved or diminished the potency of the analogues

compared to somatostatin depending on whether the pro -S or pro -R position of the amino acids was methylated.¹⁴ No obvious trends that would allow prediction of binding effectiveness were discovered or exploited in this study, but the ability of conformational restraints to effect both topography and binding was well established.

1.2.5. Cyclic amino acid and dipeptide mimics as conformational restraints.

1.2.5.1. Lactam bridged dipeptide mimics.

Some of the most effective recent work in cyclic conformational constraint involves lactam bridged dipeptide mimics. These mimics, unlike proline, link two residues so they are capable of directly affecting the orientation of both side chains in the dipeptide, thereby offering rigidity to the backbone without loss of an interaction site.

Freidinger was one of the first researchers to investigate lactams as conformational restraints in peptides. He designed and devised synthetic procedures for lactam bridged dipeptides of the type in Figure 3.¹⁵ He incorporated one of these dipeptides (N = 1) into an analogue of luteinizing hormone-releasing hormone (LH-RH). The conformationally constrained analogue was 8.9 times more potent *in vitro* than LH-RH and was also more potent *in vivo*. Freidinger attributed increased potency to improved receptor binding as a result of the pseudodipeptides' conformational restriction, and he proposed that these cyclic molecules initiated a β -turn which was complimentary to receptor binding sites.¹⁶

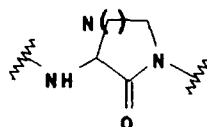
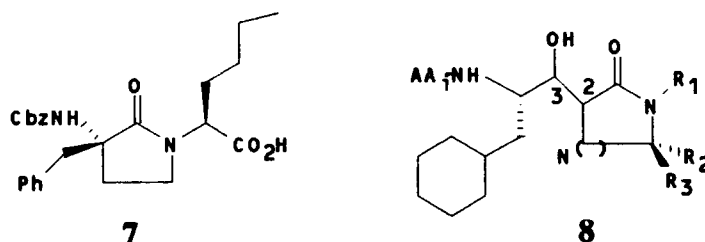


Figure 3

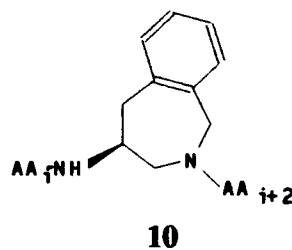
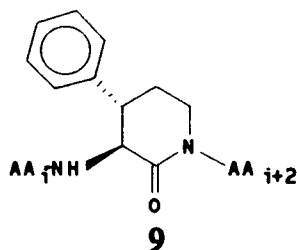
γ - Lactam bridged dipeptide isosteres based on compound **7** were modeled and suggested recently as possible restrictions at the P2-P3 site of human renin in 1988. They were successfully incorporated into the P3-P2 site of a renin inhibitor that included a hydroxyethylene transition state analogue at the P1-P2 position. The restricted inhibitor was four fold more potent than the corresponding acyclic analogue, inhibiting human plasma renin with an IC_{50} value of 6.5 nM as opposed to 26 nM for the acyclic case. The same P2-P3 site dipeptide mimic, however, actually reduced binding by two orders of magnitude over the acyclic analogue in another inhibitor that included a statine transition state analogue at the P1-P2 position (IC_{50} at 10^{-5} M compared to 10^{-7} M).¹⁷



A series of renin inhibitors with lactam-bridged P1-P1' dipeptide mimics based on the statine analogue 4(s)-amino-5-cyclohexyl-3(s)-hydroxypentanoic acid (ACHPA) **8** were designed and studied by Williams at Merck. Effectiveness of

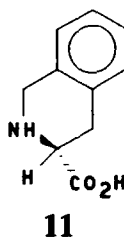
inhibition was found to depend on: (1) ring size [IC_{50} (N = 1) < IC_{50} (N = 2) < IC_{50} (N = 3)]; (2) substitution at R_1 , R_2 and R_3 (tolerating moderately sized groups such as $-CH_3$, $-CH=CH_2$, and $-CH_2CH_3$ at all positions without much degradation in activity); and (3) stereochemistry at C2 and C3 (S,S decidedly preferred to R,S or S,R). The best lactam bridged inhibitors exhibited K_i values on par with their non-constrained analogues with an IC_{50} of 1.3 nM against human renin for the best cyclic case and 1.5 nM for the best non-constrained analogue, but it should be noted that none were better renin inhibitors.¹⁸

Laszlo investigated 3-amino-4-phenyl-2-piperidinones **9** and 4-amino-2-benzazepin-3-ones **10** as conformationally restricted phenylalanine isosteres at the P2-P3 site on renin. Good inhibition was achieved (IC_{50} = 21 nM for best cyclic inhibitor), but the best cyclic mimic was 25 times less potent than its acyclic analogue. The size of the R group at the N-terminus was found to be important for bioactivity with N-acetyl derivatives being more potent than N-BOC. Molecular modeling studies indicated that the larger N-terminal group would interfere sterically with the binding process, and the results of the binding studies support that conclusion.¹⁹



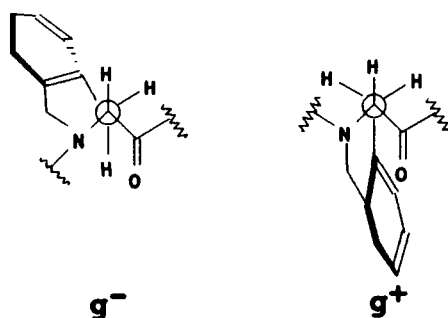
The overriding theme in the above lactam-bridged cases is one of parity with non-constrained analogues in inhibition studies and promise as probe templates for site mapping and binding studies. If a conformationally restricted mimic like the above β -lactam can be established as an effective inhibitor, then the conformationally restricted side chain's size and properties can be varied to probe or map the steric and electronic features of the enzyme subsite pocket. The ability of researchers to modify activity by introducing a lactam-bridged conformational constraint has been well established by these recent studies.

1.2.5.2 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) as a constrained phenylalanine mimic.



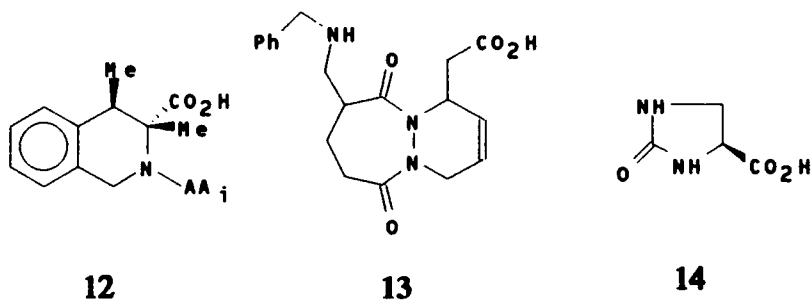
D-Tic **11** was designed by Hruby to constrain both χ_1 and χ_2 of the Phe moiety of a μ opioid receptor to a g^- conformation in the development of the most μ vs ρ selective compound known to date (9000 fold selective). Scheme 1 sets forth the two possible conformations for the side chain of D-Tic.

SCHEME 1



Analysis of NMR coupling constants between the $C\alpha$ and $C\beta$ hydrogens of a CTP receptor antagonist with D-Tic incorporated in place of Phe revealed that the D-Tic aryl side chain exists exclusively in the g^- conformation.²⁰

In an interesting development, the D-Tic residue was found to prefer the g^+ conformation when it was inserted into an interchain position instead of the N-terminal positions studied above.²¹ α,β -Dimethylation of the pipecolic acid ring was found to stabilize the g^- conformation for N-acylated α,β -dimethylated Tic derivatives per the example of (3R,4R)-D-Tic (12) so that both g^- and g^+ orientations could be achieved inside pseudopeptide chains.²²



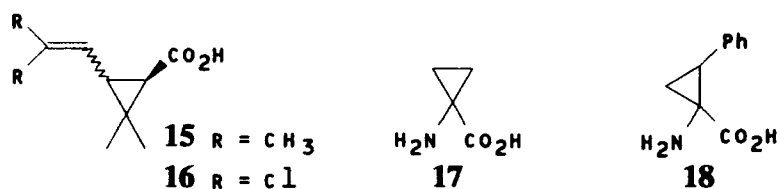
1.2.5.3 Other cyclic constraints.

Kahn inserted bicyclic heterocycle **13** into a moderately active HIV protease inhibitor at the P2-P3 sites and achieved 26 nM inhibition in vitro.²³ He has proposed this β -turn dipeptide mimic as a foundation for examination of protease secondary structure specificity. As will be discussed later in detail, the size of this bicyclic compound probably would limit its effectiveness as a probe template to the poorly defined S3 and S3' subsites in the HIV protease.

Hayashi has developed a cyclic imino acid moiety **14** that incorporates a ureido group as the C-terminal group for effective ACE inhibitors. The ureido carbonyl group provides enhanced hydrogen bonding to the enzyme because the urethane function polarizes the C-O bond more effectively than a normal amide causing a higher charge density at the oxygen and the five membered ring provides conformational restraint.²⁴

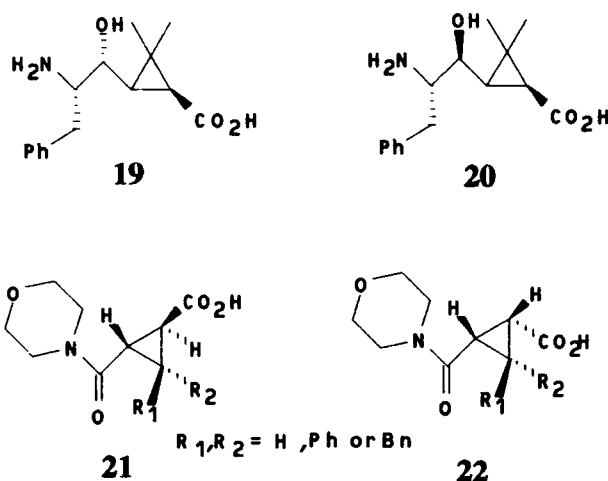
1.2.5.4. Cyclopropanes as conformational restraints.

Early interest in cyclopropanes as a conformational restraints in biological systems centered around studies of pyrethroid insecticides which incorporate cysanthamic acid **15**. The importance of this cyclopropane moiety in molecular recognition in these compounds is demonstrated by the improved potency and selectivity of insecticides containing optically active 1R-trans-cysanthamic acid and 1R-cis-permethric acid **16** over racemic compounds. The 1R-trans enantiomer apparently orients the methyl groups and the pseudo peptide backbone in a biologically active configuration that is not preferred by the 1S-trans configuration or acyclic analogues.²⁵



A group of Czechoslovakian researchers attempted to replace proline in oxytocin analogues with 1-aminocyclopropane-1-carboxylic acid **17** (Acc) to enhance uterotonic activity over that of oxytocin. Substitution of Acc for proline in these analogues lowered biological activity. Since the conformational restriction imposed by **17** does not mimic common backbone configurations for turns or sheets, this result should have come as no surprise.²⁶ Acc (**17**) has also been incorporated in enkephalin analogues, oxytocin analogues, aspartyl dipeptides, carboxypeptidase A inhibitors and tetra Acc β -sheet templates with some success. Enkephalin analogues with Acc replacing a Gly residue and oxytocin analogues have either enhanced or caused no change in potency. The best carboxypeptidase A inhibitors exhibited a K_i of 8×10^{-4} M with inhibition occurring about 2.3 times faster than hydrolysis of the substrate, but no comparisons were made to linear analogues. Cyclopropyl amino acid **18** was used to mimic Phe in position 4 of enkephalin where it enhanced opioid receptor selectivity. Aspartyl dipeptides containing Acc were sweet tasting and compound **18** was also incorporated in analogues of aspartate in an unsuccessful attempt to map "sweetness receptors".²⁷

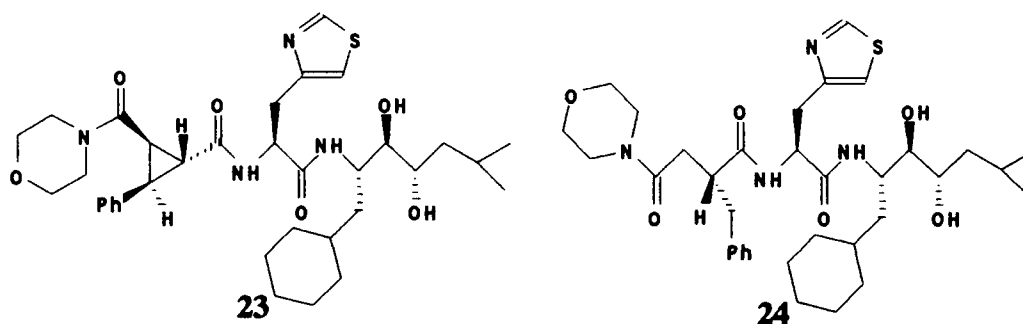
Melnick and co-workers at Upjohn proposed dimethylcyclopropane valine mimics at P1 and P1' sites on protease dipeptide transition state mimics **19** and **20**. These compounds were synthesized but results of inhibition studies are unpublished.²⁸



Ohfuné developed L-α-(carboxycyclopropyl) glycines as conformationally restricted analogues of L-Glu. He synthesized four diastereomers and conducted *in vivo* tests of neurotransmitter action in isolated rat spinal cord. The (2S, 3R, 4S)-isomer activated the N-methyl-D-aspartic acid (NMDA) subtype receptor more than established agonists did.²⁹

1,2,3-Trisubstituted cyclopropanes **21** and **22** were incorporated as combined N-terminal and P3 replacements in a series of renin inhibitors and tested for inhibitory potency in what is, to date, the most complete and elegant study of cyclopropanes as conformational constraints. Compounds **21** and **22** were designed to mimic extended β-sheet backbone conformation and fix the χ_1 angle of the aryl residue. Inhibitor **23** rivaled the most potent flexible inhibitor **24** in activity, and indications are that the conformationally constrained P3 replacement **23** mimics the topography at P3 of the bioactive conformation of its flexible analogue and the L-

phenylalanine at the P3 site of the substrate. By modifying stereochemistry and substitution around the cyclopropane ring in a series of 10 inhibitors, potency could be varied by a factor of 10. Furthermore, L-amino acid mimics were generally better than D-amino acid mimics, and L-Phe substituted mimics were better than their benzyl analogues.³⁰ Although the constrained inhibitors "tied" the flexible inhibitors in potency in this study, it is evident that substituted cyclopropanes can serve as templates from which to map the renin S3 subsite.



1.2.6. Conclusion of Conformational Restraint Review.

Substituted cyclopropanes were selected as conformational restraints in this study because they fix both ϕ (extended β -sheet or bend) and χ (g^- or g^+ , or *anti*) at angles desired in HIV protease inhibitors without sacrificing the interaction of a residue at a crucial subsite. They have established efficacy in renin and are available through relatively convenient enantioselective pathways. Potential drawbacks of this selection include the loss of an amide N-H (replaced by C2 of the mimic) for hydrogen bonding. This was compensated for in our mimic design by proposing a benzyl amide end group to replace the carboxy benzyl of an effective inhibitor.

Conformational restrictions, in general, have proven useful in peptide chemistry particularly in opioid receptor and LH-LR studies, but their performance to date in protease inhibition studies has been parallel to acyclic analogues in all but the one case discussed in Section 1.2.5.1. Perhaps the topology required of an aspartic protease is more restrictive than for the opioid receptors, and researchers need to more exactly match the bioactive conformation to achieve advantages in potency.

1.3. Human Immunodeficiency Virus Protease.

Human immunodeficiency virus (HIV) is the cause of acquired immune deficiency syndrome (AIDS). HIV-1 is a retrovirus in the Retroviridae family and belongs to the sub-family lentivirinae [lenti is Latin for slow referring to the long incubation period] along with the viridae that cause encephalopathies, pneumonitis, arthritis, and hemolytic anemia. HIV contains a small RNA genome which is translated into DNA in the host cell by reverse transcriptase, a DNA polymerase brought to the host by the viral particle. Another essential enzyme, integrase, then aids in inserting the HIV DNA genome into the host DNA. The host cell then produces large polyprotein precursors for core (**gag**), envelope (**env**), and polymerase (**pol**) proteins. These precursors are processed by the HIV protease to yield the structural proteins and enzymes of the mature viron.³¹ The protease is essential for viral replication and is a popular therapeutic target in current drug research.³² It also serves as an excellent platform for molecular recognition studies

because of its relative simplicity and the large amount of information available on its structure.

1.3.1. HIV-1 protease structure.

Recombinant DNA techniques and total chemical synthesis have been used to produce HIV-1 protease because isolation of the natural protease is dangerous and yields only minute quantities of material.³³

From X-ray crystal structures and other work, the HIV protease has been determined to be a 99 amino acid aspartic protease with a molecular weight of 27 KD. In its native active form, it is a homodimer with "flaps" over an Asp-Thr-Gly active site.³⁴ Figure 4a shows an X-ray crystal structure of the protease dimer with one monomer colored red and the other colored blue. A bound inhibitor (green) is included to highlight the flaps over the active site. Figure 4b shows a cut-away view of the one monomer with bound inhibitor. The residues involved in the dimer junction are colored purple. The enzyme has a rough C2 symmetry, and subsites S2 through S2' are well defined. S3 and S3' sub-sites are less conspicuous and are exposed to solvent in this relatively narrow enzyme.

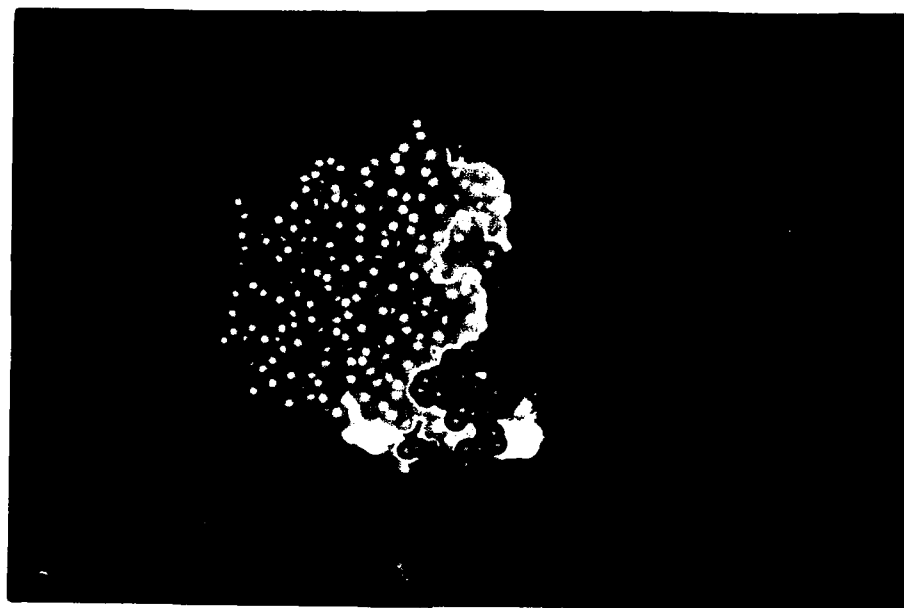


Figure 4a

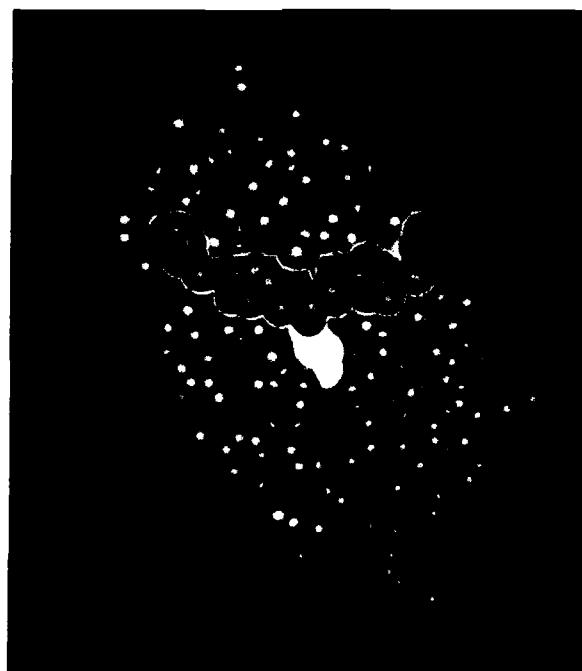
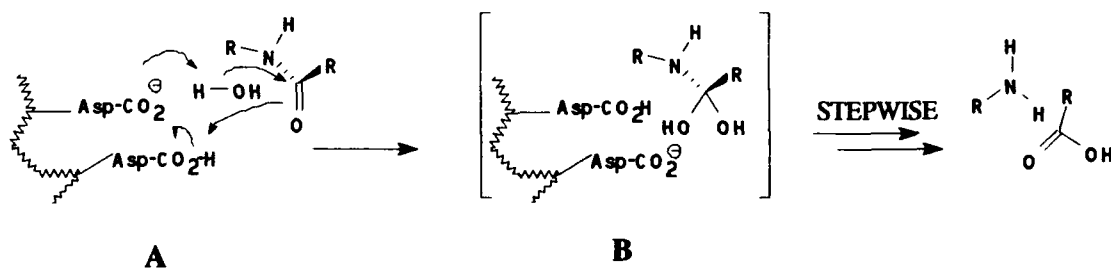


Figure 4b

1.3.2. HIV-1 protease function.

One proposed mechanism for aspartic protease cleavage mechanism involves the two Asp residues at the active site and a water molecule as set forth in Scheme 2.³⁵ The transition state between the "just bound" conditions described in situation A of Scheme 2, and intermediate state B, in which the carbonyl carbon has been transformed to a diol, is suspected to be tetrahedral in nature. This mechanism is based on the concept that the transition state geometry about the scissile bond is bound more tightly than the substrates natural amide bond geometry thereby lowering the activation energy of the cleavage reaction. The tetrahedral nature of the transition state is an important feature of this proposal and is exploited in a variety of transition state inhibitors.

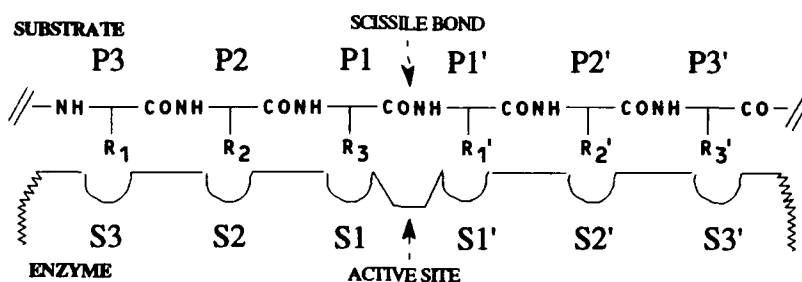
SCHEME 2



Substrate specificity of the HIV protease is very broad, and substrate sequences have been classified into three groups depending on residues present at P1' and P2' in Table 1.³⁶ Some trends can be observed: (1) Phe and Tyr are

common at P1; (2) Pro, which is not normally accommodated in the P1' position of other proteases such as trypsin, is found in three of the eight sequences at P1'; (3) there is a general trend toward hydrophobic residues at P2' and P3'; and (4) P2 and P2' both accept Ile, a branched non-polar residue.³⁷

Table 1



Classification of HIV-1 Protease Substrates

Class A

P3	P2	P1	P1'	P2'	P3'
Gln	Asn	Tyr	Pro	Ile	Val
Phe	Asn	Phe	Pro	Gln	Ile
Leu	Asn	Phe	Pro	Ile	Ser

Class B

Thr	Ile	Met	Met	Gln	Arg
Gly	Asn	Phe	Leu	Gln	Ser
Gln	Ala	Asn	Phe	Leu	Gly
Lys	Ile	Leu	Phe	Leu	Asp

Class C

Arg	Val	Leu	Ala	Glu	Ala
-----	-----	-----	-----	-----	-----

In a more recent analysis of HIV proteinase subsite preferences researchers found that: (1) subsites S1 and S1' showed explicit preference for hydrophobic residues; (2) β branched amino acids and Pro were not tolerated at S1; and (3) S2 showed a preference for small polar and apolar residues. All amino acids could be

accommodated at S3, which is consistent with graphical analysis of subsite size and composition based on X-ray data and other residue substitution studies that indicate that the P2 through P2' residues are critical in binding to the enzyme.³⁸

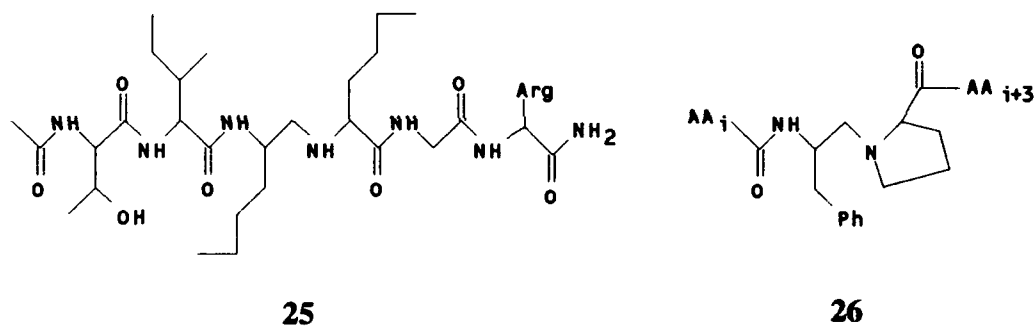
One interesting study by Tommasselli showed that HIV protease degraded actin, troponin, and Alzheimer amyloid precursor protein (AAP). Although it was proposed that the protease could possibly damage regulatory and structural cellular proteins, there was no mention of studying the effect of AIDS on victims of Alzheimer's disease.³⁹

1.3.3. HIV protease inhibitors: Transition State Mimics.

Transition state (TS) mimics have been designed on the premise that the enzyme accelerates the cleavage of the scissile bond by binding more tightly to the transition state than to the substrate as discussed in Section 1.3.2. above. By mimicking the tetrahedral nature of the scissile bond carbonyl carbon at the transition state, researchers hope to both enhance binding and substitute a non-labile bond to inhibit the protease cleavage. Four major categories of HIV protease inhibitors based on transition state mimics are reduced amides, hydroxyethylene isosteres, di-hydroxyethylene isosteres and hydroxyethylamines. Each of these categories is discussed in detail below. Phosphinates, α,α -difluoroketones, and non-peptide inhibitors have also been used as tetrahedral TS mimics but were not considered as templates for our conformational restriction studies because there is no crystallographic information on the bound configuration of these molecules.⁴⁰

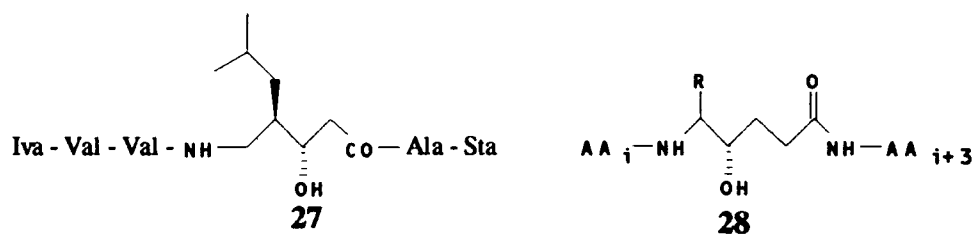
1.3.1.1. Reduced amides.

Compounds like **25** were designed based on the concept that reducing the carbonyl of the substrates scissile bond of a substrate analogue prevents cleavage of the acyl-nitrogen bond and establishes a tetrahedral center as a TS mimic at the carbonyl carbon. Compound **25** (MTV-101) inhibited well enough to give the first bound inhibitor/protease crystal structure ($K_i = 1.4 \mu\text{M}$), but in general the best reduced amide inhibitors exhibit micromolar K_i 's.⁴¹ More recently, inhibitors with the core structure **26** were made and tested by Cushman with K_i 's, for the best compounds inhibiting at micromolar levels.⁴²



1.3.3.2. Hydroxyethylene isosteres.

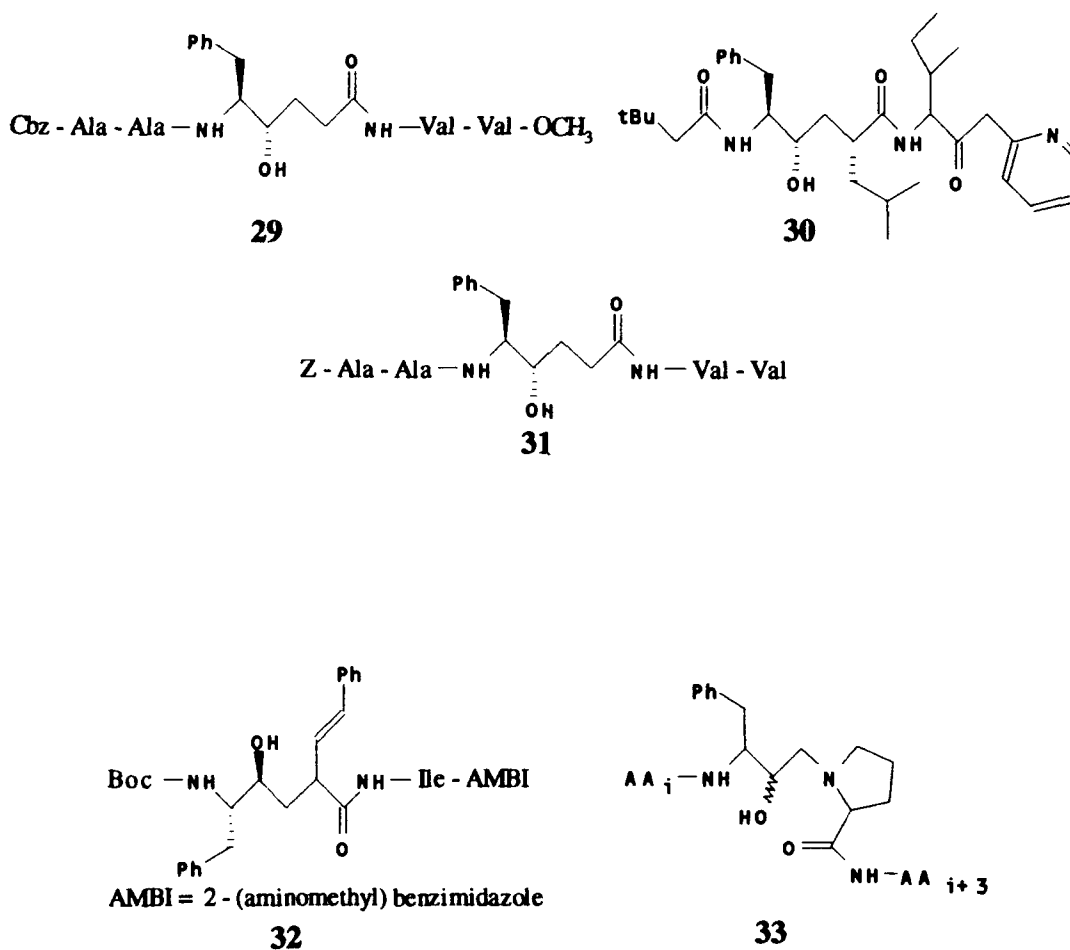
Pepstatin (**27**) is a known inhibitor of aspartic proteases and does exhibit moderate activity against HIV protease. Early inhibition studies used this compound as a standard for inhibition assays, and the Statin (Sta) unit has been used as a transition state replacement in some recent studies despite its relatively poor inhibition record (μM K_i 's at best).⁴³



Extending the pepstatin backbone of compound **27** by a methylene group to form a hydroxyethylene isostere maintains dipeptide backbone spacing, and mimics the Xxx-Gly dipeptide. The hydroxyethylene isostere **28** is a more effective HIV protease inhibitor than the statine analogue by a factor of 10^3 . Compound U-85548E (**29**) was found to inhibit HIV protease with $K_i = 48$ nM.⁴⁴ Later studies of this compound showed poor inhibition of HIV protease in cell cultures, but a similar compound U-81749 **30** was found to exhibit a $K_i = 70$ nM and an $\text{IC}_{50} = 0.1$ μM in cell cultures.⁴⁵ Dreyer made and conducted HIV protease inhibitor studies on a series of substrate analogues with hydroxyethylene isostere inserts. He discovered that compound **31** was the best inhibitor with a K_i of 18 nM and that its analogue with S stereochemistry at the hydroxyl carbon inhibited better than the R version. He proposed that the hydroxyl in the bound inhibitor with S stereochemistry at the hydroxyl carbon is positioned between the two aspartate groups at the active site, replacing the bound water that would normally interact in this position. Apparently the R configuration does not mimic this configuration as well.⁴⁶

In a most impressive study, hydroxyethelene inhibitors of the type **32** with a 3-phenylprop-2-ene ligand at P1' were found to have sub-nanomolar IC_{50} 's and were active against HIV protease in inhibition studies and in cell cultures.

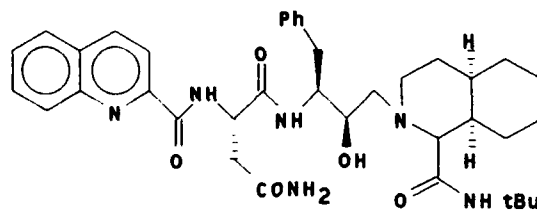
Interestingly, compound **32** restricts χ_2 at P1'.⁴⁷ The success of the S configuration at the hydroxyl carbon in this compound supports Dryer's proposal above.



1.3.3.3. Hydroxyethylamine isosteres.

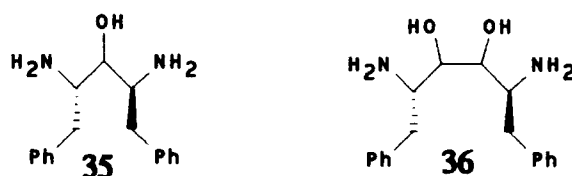
The hydroxyethylamine mimic of Phe-Pro is illustrated in compound **33**. The methylene inserted between the hydroxyl carbon and the nitrogen extends the dipeptide backbone by one carbon, but it allows incorporation of normal amino

acids at P1' with N-H hydrogen bonding intact for primary amino acids. Roberts rationally designed the hydroxyethylamine analogue **34**, which exhibited subnanomolar IC₅₀ concentrations, and used this transition state mimic to probe active sites on the protease. Based on inhibition studies with a series of 15 compounds, he determined that a tripeptide was needed for optimum activity. There were also indications of a large hydrophobic pocket at S3' (to accommodate the decahydroisoquinoline (DIQ)). The Asn residue was best at P2, and a benzyl substituent was best at P1. The R configuration at the hydroxyl carbon was found to be more effective than the S (opposite of the results for the hydroxyethylene examples above).⁴⁸ Comparison of compound **34** to the hydroxyethylene-based compound **31** reveals that **34** has an extra methylene in the backbone between P1 and P1'. This longer backbone chain in the active site area may explain the preference for R stereochemistry at the hydroxyl carbon. Research on a series of similar compounds incorporating the same transition state isostere as **34** found the R configuration to be effective. The report on these compounds concludes that the DIQ residue acts as a proline mimic.⁴⁹ The DIQ can also be considered a cyclic χ' constraint for the cyclohexyl group in DIQ and the crystal conformation illustrated in the article shows a g^- conformation for the bound DIQ cyclohexane.

**34**

Rich designed eight analogues of **33** above to mimic the HIV protease substrates p17 and p24. They were tested against similar compounds with statine

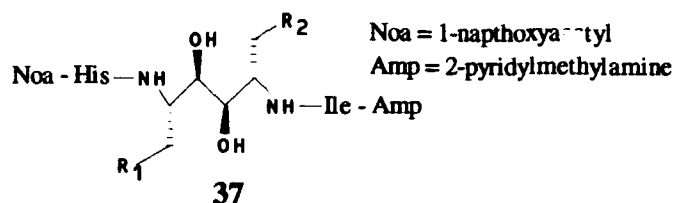
and hydroxyethylene (HEA) isostere inserts. The hydroxyethylamines were found to be significantly better inhibitors.⁵⁰ In a surprise result, the S diastereomer of the most potent of these analogues crystallized selectively with the protease; this result is consistent with the superior binding of the S diastereomer relative to the R. Since this result directly conflicted with Robert's results above, a closer investigation ensued. Molecular modeling and analysis of crystal structure indicates that the tert-butyl end group of the DIQ in **34**, and not the DIQ cyclohexyl moiety, binds at the S2' subsite causing a modification of backbone configuration that favors the R configuration.⁵¹ The debate over the most effective transition state geometry for HEA inserts is still active, but it is apparent that the interactions of residues away from the active site with enzyme binding sites may influence the S or R preference.



1.3.3.4. Dihydroxyethylene isosteres.

Abbott designed the symmetrical diamino alcohol **35** and diaminodiol **36** based on the pseudo-C₂ axis of the HIV protease. Both were highly effective when acylated with Cbz-Val groups (IC₅₀ = 3.0 nM for **35** and < 0.38 nM for all three diastereomers of **36**). All of the diaminodiol analogues inhibited HIV in cell cultures.⁵² Ghosh and co-workers have subsequently developed a stereocontrolled synthetic route to the diaminodiol dipeptide isostere **36** from D-mannitol.⁵³

Workers at Upjohn stereoselectively synthesized analogues of **37** with cyclohexyl, isopropyl or phenyl substitution at R_1 and R_2 . These compounds exhibited K_i 's ranging from 1 to 26 nM. Variations in stereochemistry at C2 and C3 of the isostere demonstrated that the absolute stereochemistry was vital for biological activity. One diastereomer was 30 times less potent than the other three. There is however no clearly preferred diastereomer for the dihydroxyethylene isostere since three of the four tested inhibited with K_i 's around 1.5 nM.⁵⁴



Overall, dihydroxyethylene (DHE) and hydroxyethylene (HE) isosteres are the most promising of the transition state mimics based on performance. The interaction of HE isosteres is fairly well understood, but the binding geometry of the DHE's is not known. The two hydroxyls may replace one or both the water molecules that are normally bound at the active site with a substrate.

1.4. Bound inhibitor crystal studies.

X-ray crystal analysis of aspartic proteinase/statine based renin inhibitors by Blundell in the late 1980's established two important facts about protease inhibitors that have been consistent through all reported HIV protease/inhibitor complexes. The inhibitors bind in an extended β -strand conformation in the active site cleft, and the hydroxyl of the transition state analogue interacts strongly with the catalytic

aspartate residues via hydrogen bonds.⁵⁵ These observations have become the basis for current rational inhibitor design in renin and HIV protease studies as well as other aspartic proteases. We studied five reported HIV protease/inhibitor complexes (MTV-101, A-74704, JG-365, U-85548e, and L-700,417) in our design process. Coordinates for MTV-101 at 2.3 Å and A-74704 at 2.8 Å were made available to us by Dr. Alexander Wlodawer at the NCI-Fredrick Cancer Research Facility and the Department of Anti-infectious Research at Abbott Laboratories. Literature reports on the other complexes were compared to graphical data available on MTV-101 and A-74704.

1.4.1. The MTV-101 complex: A reduced amide isostere.

This complex of MTV-101 and chemically synthesized HIV-1 protease was reported first at 2.3 Å and later at 2.0 Å resolution.^{36,56} MTV-101 (Compound **25**) bound to the enzyme in extended β -strand configuration as indicated in Figure 5. Norleucine residues at P1 and P1' are extended into hydrophobic pockets at S1 and S2. Ile and Gln occupy P2 and P2' respectively, but the Thr residue at P3 is in the solvent channel; the Arg at P3' binds to the outside surface of the enzyme. At the active site there is no interaction with the enzyme aspartate residues because there is no carbonyl or hydroxyl in the TS mimic.

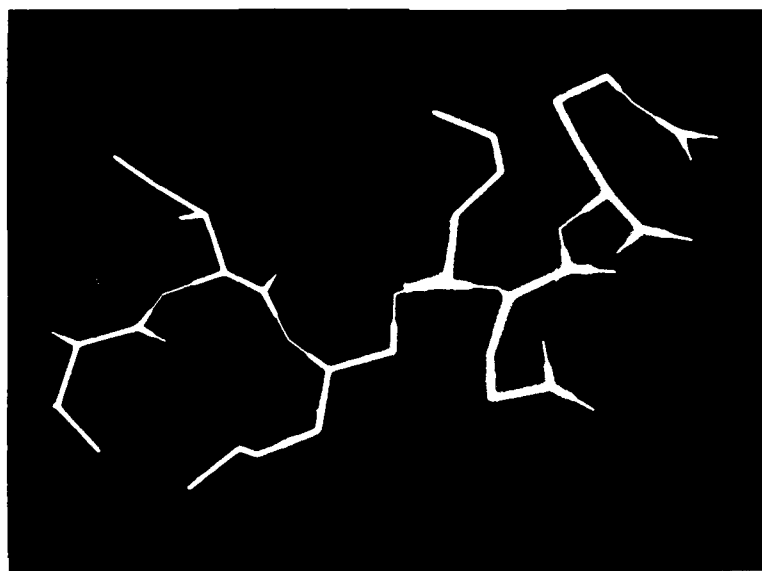


Figure 5

The most interesting aspect of Wlodawer's study was the discovery of extensive enzyme conformational changes on binding to an inhibitor. Binding caused a hinge motion of 1.7 \AA with the hinge at the inter-subunit β -sheet interface. This motion tightens the active site cavity. Two flaps extend over the active site enveloping the inhibitor as can be seen in figure 6a and 6b. In the native enzyme the flap of the bottom subunit is over that of the top. This arrangement reverses in the bound inhibitor complex with the tips of the flaps moving more than 7 \AA in the binding process. A review of the hydrogen bonding interactions in the crystal complex indicates no interaction at the active site; this is probably one reason that this inhibitor, like other reduced amides, inhibits only on a $\mu\text{M } K_i$ scale.

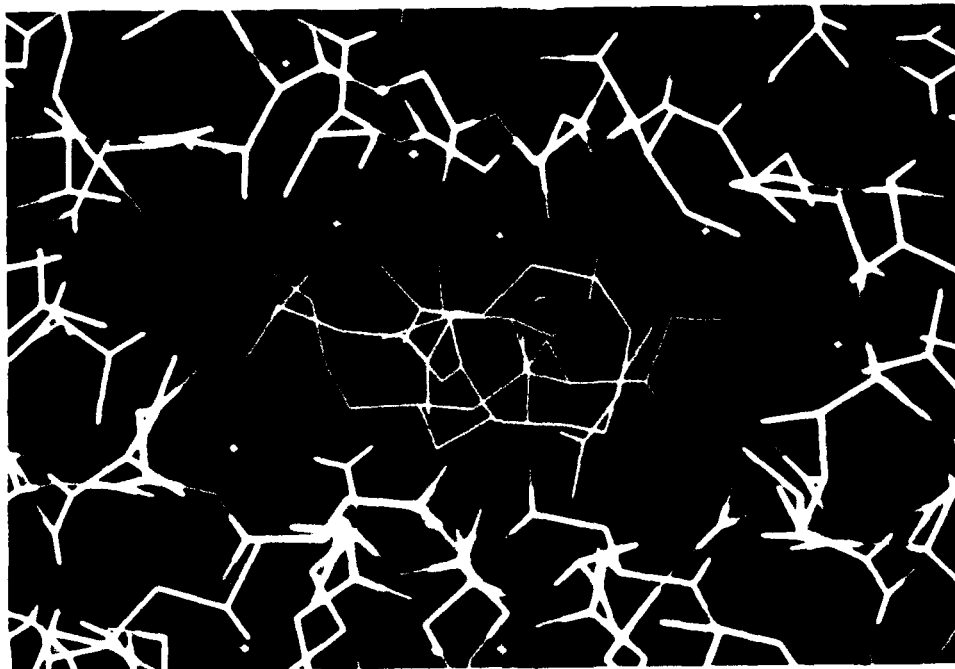


Figure 6a

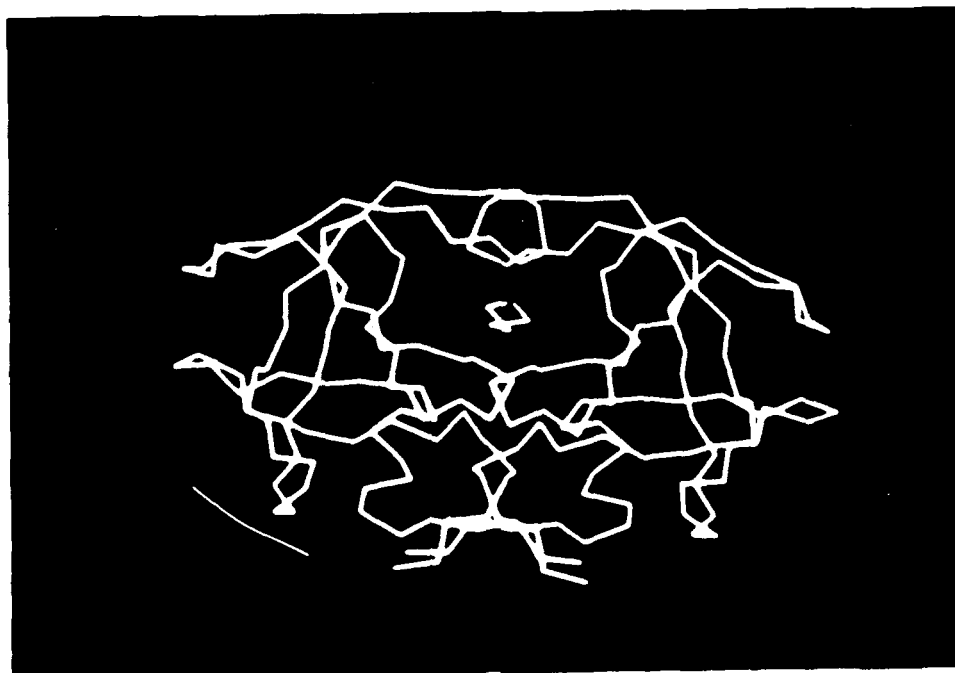


Figure 6b

1.4.2. The A-74704 Complex: A diamino alcohol isostere.

This complex between the two-fold (C_2) symmetric inhibitor and the HIV-1 protease was reported at 2.8 Å.⁵⁷ The inhibitor is bound in a stair-step extended β -sheet configuration with a rough C_2 axis as shown in Figure 7a and 7b (inhibitor in green). These figures also accentuate the narrow nature of the enzyme and its relatively small size. P3 through P3' residues bind in roughly the same enzyme subsites as MTV-101 but are involved in more hydrophobic interactions per Table 2. The inhibitor has the same number of predicted hydrogen bonds to the enzyme as MTV-101 except that hydroxide moiety hydrogen bonds to the active site aspartates. The increased number of hydrophobic contacts and the extra hydrogen bonding at the active site may explain the lower K_i of A-74704 when compared to MTV-101 (4.5 nM vs 700 nM) but the use of different assays tends to confuse this argument significantly. Figure 8 demonstrates that the flaps in this complex behave in a manner similar to that observed in the MTV-101 complex.



Figure 7a

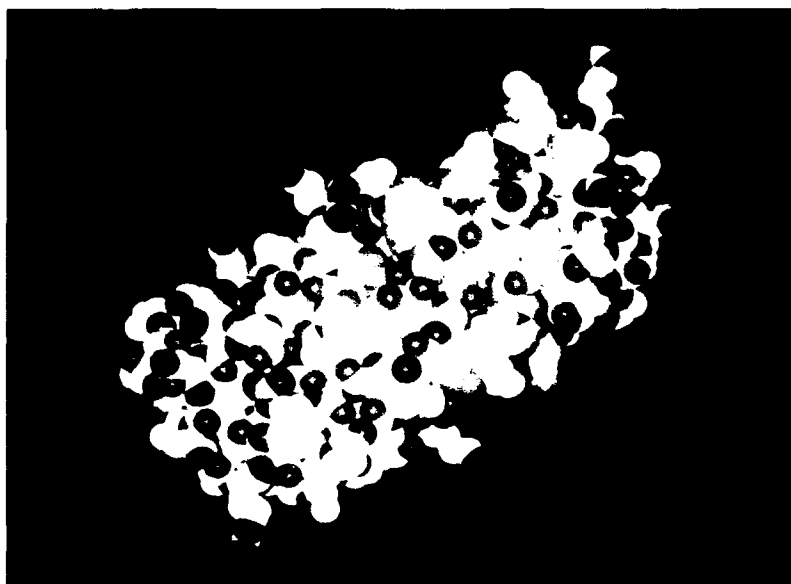


Figure 7b

Table 2

Enzyme residues within 4.2 Å of ligand

<u>subsite</u>	<u>A-74704</u>	<u>MTV-101</u>
S2	7	4
S1	8	6
S1'	10	7
S2'	9	4

1.4.3. Other inhibitor complexes.

Wlodawer reported an inhibitor/HIV-1 protease complex for JG-365 (Compound **38**) with a 0.24 nM K_i . This inhibitor was also bound to the enzyme in an extended β -strand configuration with stereochemistry at the hydroxyl carbon. H-Bonding and hydrophobic interactions were found to be better than MTV-101.⁵⁸

Apparently the extra hydrogen bonding by the hydroxyl at the active site and the larger benzyl residues at P1 and P1' afford binding advantage.

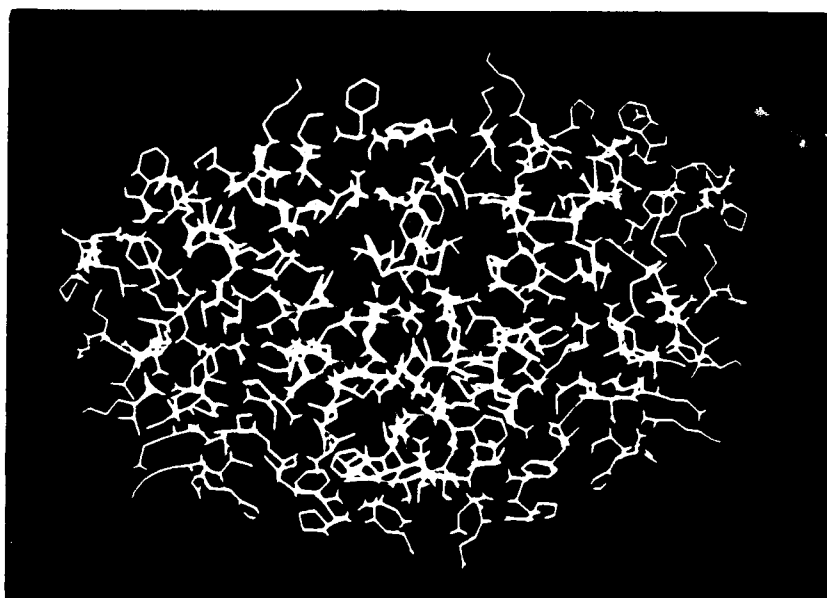
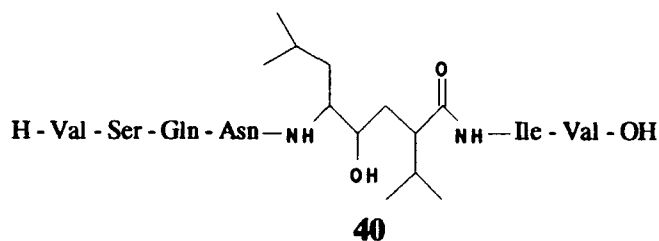
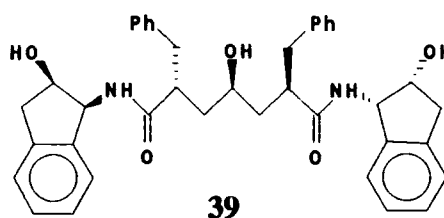
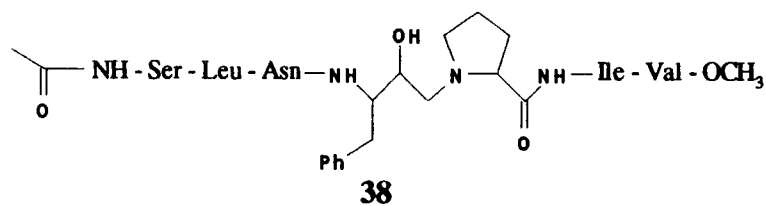


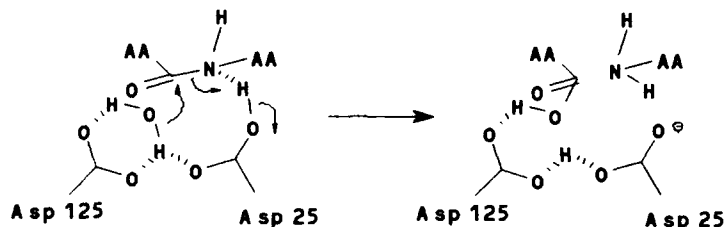
Figure 8

A crystal structure of pseudo C_2 symmetrical compound **39** bound to the HIV protease was obtained and reported. This compound exhibited a subnanomolar IC_{50} . The crystal structure indicated that the inhibitor formed fewer hydrogen bonds to the enzyme than it was capable of forming, but that hydrophobic interactions were comparable to examples above. The authors tout "efficient packing" of the P2/P2' binding sites by the large indan rings as a hydrophobic advantage.⁵⁹ However, the disrupted H-bonding pattern could be the result of backbone configuration changes caused by "over packing" these sites, which previously have been found to accommodate only small hydrophobic groups.

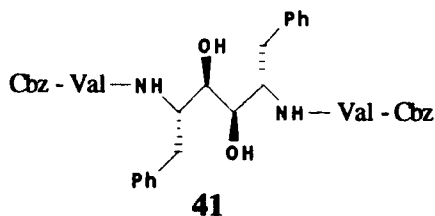


Tommaselli has reported an HIV protease crystal structure bound to the sub-nanomolar hydroxyethylene based inhibitor U-85548e (**40**). Binding was similar to MTV-101 and A-74704, and the HE isosteres general preference for S hydroxy carbon configuration was confirmed again. Based on the geometry of the active site moieties in the complex, a new concerted mechanism was proposed involving simultaneous attacks of the nucleophilic water and the electrophilic proton per Scheme 3.

SCHEME 3



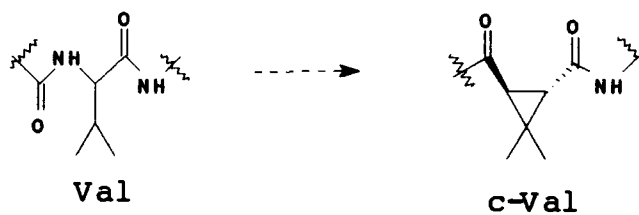
1.5. Analysis and design of conformationally constrained peptide mimics for HIV protease binding studies.



After reviewing available information on peptide conformational restrictions and HIV protease inhibition studies above, we decided to investigate substituted cyclopropanes as mimics for the P2/P2' sites of Abbott's symmetrical diaminodiol inhibitor **41**. This compound is an attractive base compound for constrained analogues because: (1) the HDE isosteres exhibit high binding affinity toward HIV protease; (2) the compound's symmetrical nature allows the same changes to be made to both ends of the molecule to eliminate binding distortions that could be caused by induced fit of the symmetric enzyme to an asymmetric inhibitor; (3) the known atomic coordinates of A-74704/HIV protease complex should serve as a reasonable P2/P2' template for mimic design; (4) the biological activity of **41** and its analogues have been extensively studied so a base of information for comparative

studies exists; and (5) researchers at Abbott agreed to provide compound **36** as starting material. Therefore, design and synthesis of the c-Val mimic of Scheme 4 and its analogues became the primary focus of this research project.

SCHEME 4



CHAPTER 2. RATIONAL DESIGN OF SUBSTITUTED CYCLOPROPANES AS PEPTIDE MIMICS.

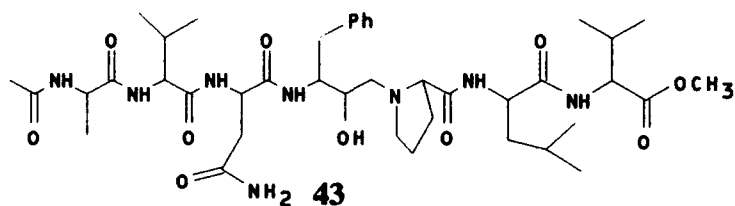
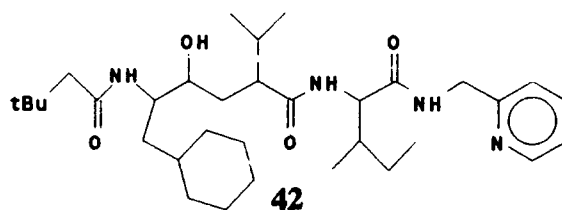
2.1. Introduction.

It is beyond the scope of this paper to provide a detailed review of molecular modeling. Kollman authored a basic review of the subject in 1987,⁶⁰ and workers at Ciba-Geigy prepared an excellent review of software and methods for medicinal chemistry in 1990.⁶¹ Guidelines for publication of computer studies are set forth in the *Journal of Medicinal Chemistry*.⁶² Our modeling was done in the SYBYL and MACROMODEL molecular modeling programs. The Tripos force field was used to model small molecules, and Kollman-united and Kollman-all force fields were used to model peptides.⁶³ Pertinent examples of computer design and analysis of inhibitors for aspartate proteases and viridae abound.⁶⁴

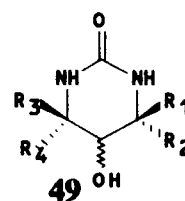
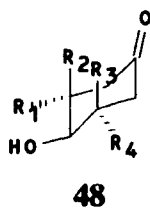
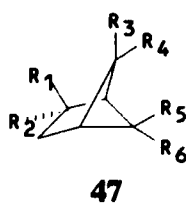
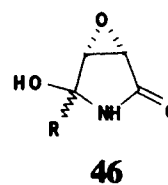
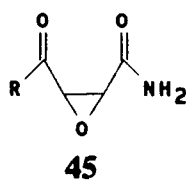
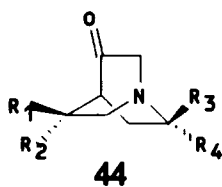
Our molecular modeling in this project was conducted in three stages. We first conducted relatively crude computer studies of known inhibitors using the enzyme/inhibitor complexes as templates. We then conducted backbone configuration analysis and χ' angle analysis of substituted cyclopropanes before proceeding to detailed comparisons of c-Val to the P2/P2' residues of bound inhibitors and designing target inhibitors for synthesis. Each of these studies is detailed below.

2.2. Conformational analysis of known inhibitors and the search for "flap water" mimics.

After a three dimensional (3-D) visual analysis of the native protein and the MTV-101/protease complex, our first goal was to determine if the most effective inhibitors reported at the time could achieve the configurations necessary to bind the HIV protease in a manner similar to MTV-101. For this study the hydroxyethylene analogue U-81749 (**42**) and Rich's best hydroxyethylamine (**43**) were modeled. An RMS fit of both modeled compounds, including backbone carbons and C β carbons from subsite P2 to subsite P2', was conducted against MTV-101 in its bound configuration. All bonds in inhibitors **42** and **43**, including amide bonds, were allowed to rotate. The extra backbone methylene in **43** was compensated for by not including the scissile bond carbons in the fit so they could move as dictated by the "binding" of P1 and P1' residues. Results were disappointing. Compound **43**'s best RMS fit to MTV-101 was 0.86 Å and an RMS fit of 0.40 Å was achieved for **42**. Both fits also involved some ϕ and ψ angles significantly different from the β -strand like values observed in MTV-101. One bright spot was that all P2-P2' residues in these two inhibitors could be sterically fit into the S2-S2' subsites on the enzyme. After a brief attempt to fit a model of **34** against MTV-101 with similar results, this project was dropped.



Substituted quinuclidones **44**, cerulinin mimics **45**, cerulinin tautomers **46**, bicyclo[1.1.2]hexanone derivatives **47**, 3-hydroxycyclohexanones **48**, and cyclic urethanes **49** were modeled and fit by manually docking them with the A-74704 in its bound conformation in an attempt to find an active site mimic that could replace both the active site nucleophilic water and the water bound between the flaps of the inhibitors to enhance binding. None of these fits were attractive enough to warrant further study.



2.3. Analysis of cyclopropane's effect on conformation.

As mentioned above, a common trait of bound aspartic protease inhibitors is they bind in an extended β -strand configuration. One graphic example of the conserved nature of this binding geometry in aspartic proteases was discovered in a preliminary computer analysis of bound inhibitor crystal structures. Rigid RMS fits of bound inhibitors such as MTV-101 and A-74704 were found to be generally close (<0.4 Å P2-P2' backbone plus C_{β}), but the P2-P2' backbone plus C_{β} RMS fit of Seguna's bound rhizopus pepsin inhibitor and Abbott's aspartic protease bound renin inhibitor A-0904 was 0.012 Å! A stereoview of this remarkable example of conserved backbone orientation is provided in Figure 9. With this encouraging discovery behind us we proceeded to local analysis of ϕ and χ angle restrictions by cyclopropane as detailed below.

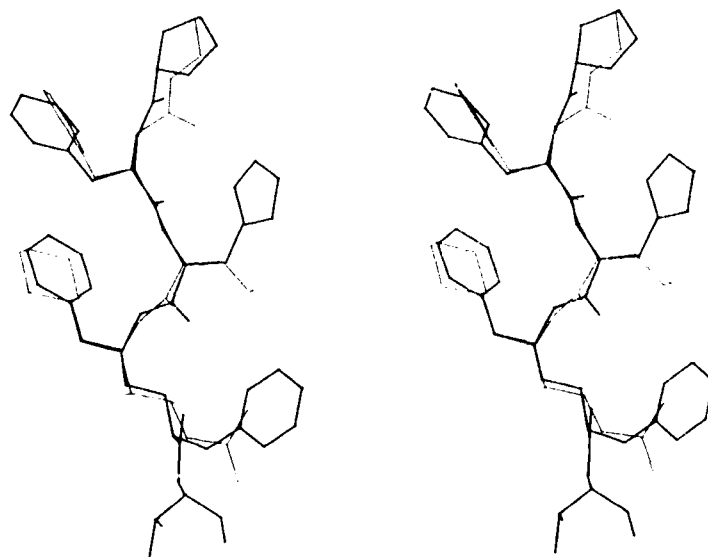
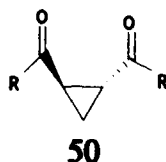


Figure 9

2.4. Cyclopropane as a ϕ -angle restrictor.



Compound **50** representing symmetrically *trans*-disubstituted cyclopropanes was fit against the backbone P2-P2' sites of the bound inhibitors MTV-101 and A-74704 to test the ability of substituted cyclopropanes to mimic the bound inhibitor residues ϕ angles. Results of backbone fits in Table 3 indicated that *trans*-substituted cyclopropanes mimic the psuedo- β -strand conformation of these two inhibitors best when incorporated at P2 and P2', and RMS fits of the $C_{i-1}-N_i-C_{\alpha i}-C_i$ sequence for cyclopropanes against amino acids in the traditional extended β -sheet configuration ($\phi = -139^\circ, \psi = 135^\circ$) were all less than 0.12 Å.

Table 3

RMS FIT (Å)

	MTV- 101	A-74704
P2	0.26	0.18
P1	0.60	0.52
P1'	0.42	0.50
P2'	0.17	0.12

These two studies indicated that the P2 and P2' site of an inhibitor would be the most attractive position to insert cyclopropane moieties in HIV protease inhibitors to investigate the effects of ϕ angle restriction.

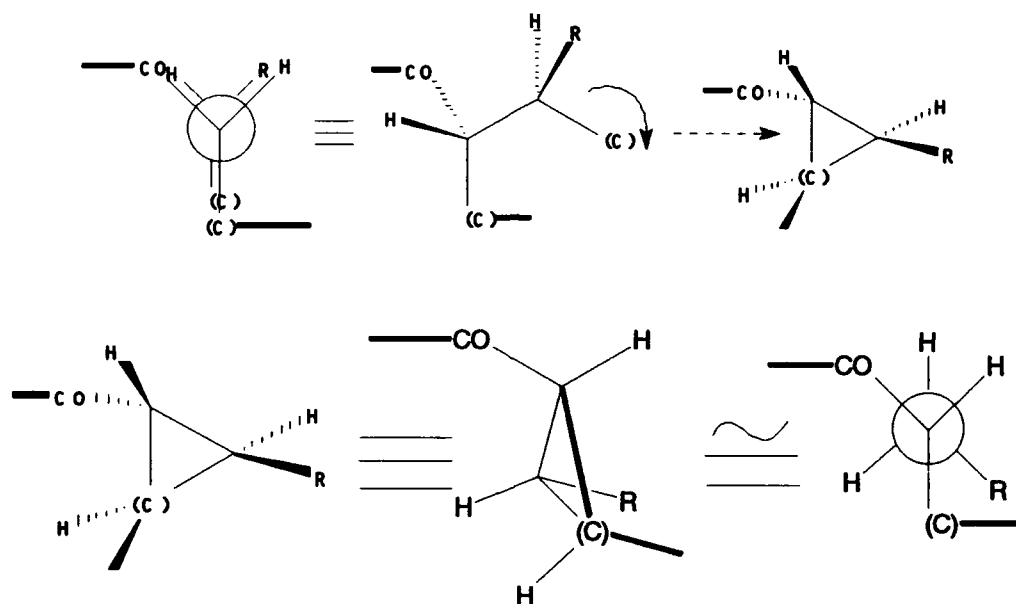


Figure 10

2.5. Cyclopropanes as χ angle restrictors.

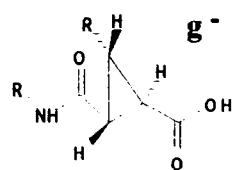
The ability of cyclopropanes to match backbone orientation and simulate a g^- conformation because of the "bent" nature of the cyclopropyl C-C bonds is illustrated in Figure 10. The (C) carbon in Figure 10 represents the cyclopropyl C2

that replaces the amino acid nitrogen when the mimic is inserted into a peptide chain. The bent (C) to C_α to C_β bond angle causes the R group to position itself at the g^- position. Using this analogy we designed substituted cyclopropane mimics **51a** and **b** to achieve g^+ and g^- configurations. We also modeled an **anti** mimic **52**, but it is a ψ angle restrictor and has not been considered in the current study. Figure 11a and 11b provide stereo views of g^- and g^+ cyclopropane mimics of Phe fit against a Phe in extended β -sheet configuration with g^- and g^+ orientations respectively. Analysis of P2 χ_1 angles in the bound configurations of two HIV protease inhibitors is detailed in Table 4.

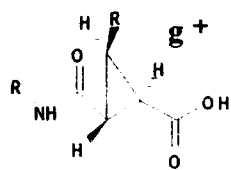
Table 4

Inhibitor	Residue	χ_1 at P2
*A-74704	Val	g^- , anti
*MTV-101	Ile	$g^+(Et)$, $g^-(Me)$

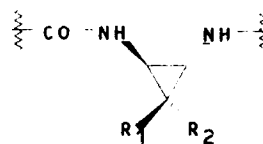
These results and visual analysis of the S2 subsite in the HIV protease indicates that there are methyl group sized "pockets" at S2 subsite in the g^- and **anti** positions of the substrate and a larger "pocket" capable of accommodating an ethyl group at the g^+ position. Figure 12 compares the orientations of free valine (preferred), bound A-70704 and MTV-101 residues, and the c-Val mimic from Scheme 4.



51a



51b



52

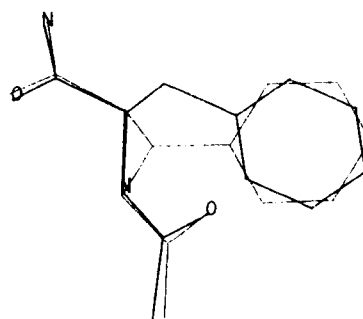
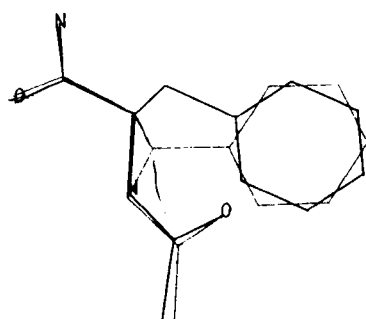


Figure 11a

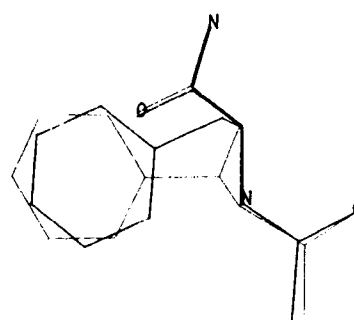
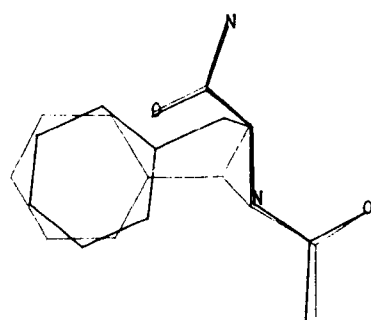


Figure 11b

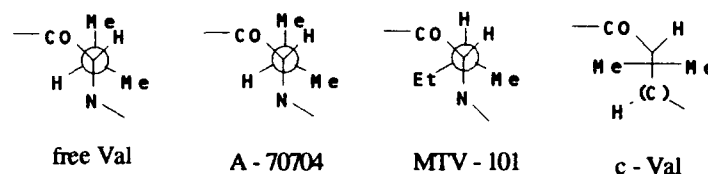


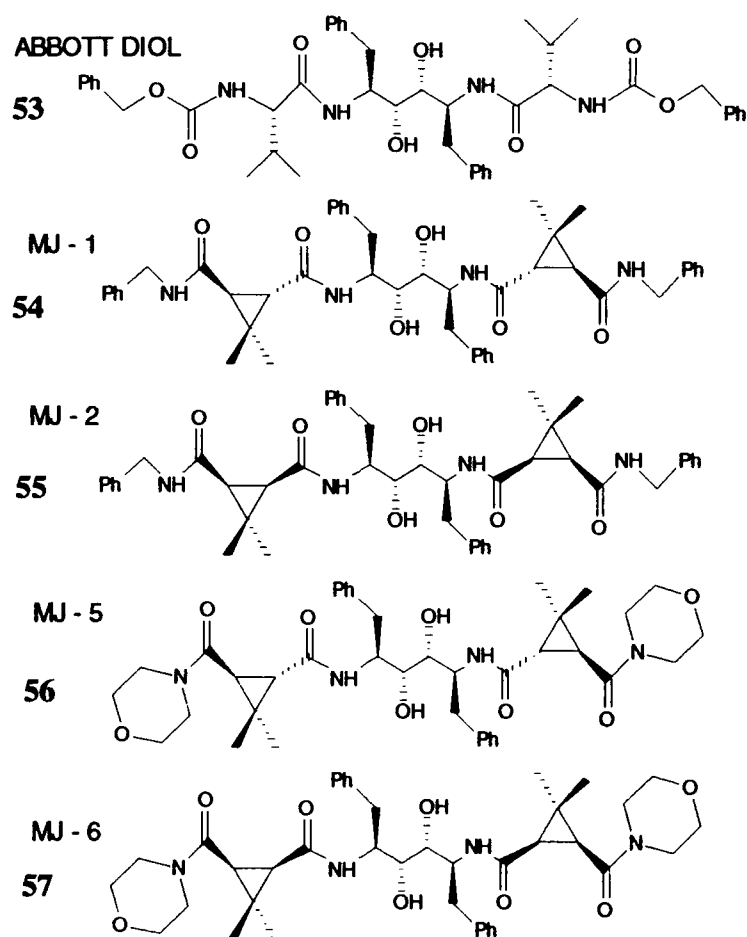
Figure 12

2.6. Conformationally constrained inhibitor design.

The Abbott diol **53** was chosen as a template for conformational restriction. Compounds **54**, **55**, **56**, and **57** represent a series of potential mimics that could be used to probe the HIV protease at the P2 subsite. Compound **54** varies from **53** only in the replacement of Val with c Val and the use of benzyl end groups instead of carboxyl benzyl end groups. The benzyl substituted amide was selected as a target over a carboxybenzyl mimic to "add back" the N-H donor lost at C2 of the cyclopropyl mimic and give **54** the potential to establish the same number of hydrogen bonds as **53**. This compound is expected to test the validity of the c-Val mimic as a replacement for Val at P2 and P2' in HIV inhibitors. Compound **55** differs from **54** by a cis configuration at cyclopropane. It is designed to validate the molecular modeling prediction of superior binding by trans-substituted compounds over cis-substituted compounds. Compounds **56** and **55** are designed to investigate the effect of replacing hydrophobic end groups with hydrophilic end groups on binding and transport.

The c-Val mimic should simulate the required backbone configuration of Val in the bound inhibitor and achieve an entropic binding advantage while

matching the hydrophobic binding potential of Val with methyl groups in 2 of the 3 P2 "pockets" described above. Synthetic routes to these mimic compounds are discussed in detail in Chapter 2.



CHAPTER 3. SYNTHESIS OF SUBSTITUTED CYCLOPROPANES AS PEPTIDE MIMICS.

3.1. Introduction.

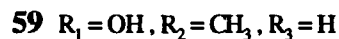
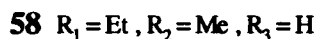
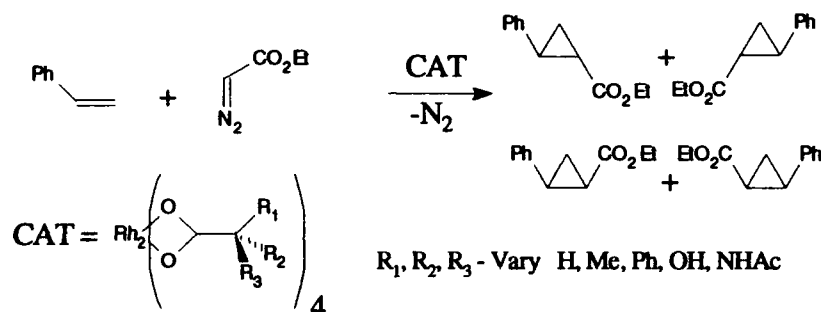
Each of the HIV protease inhibitors we designed in Chapter 2 has eight chiral centers and to properly evaluate the effects of the substituted cyclopropyl peptide mimics on HIV protease inhibition, compounds **53** through **57** must be diastereomerically pure. The establishment of eight chiral centers represents a significant synthetic challenge. Fortunately, the symmetrical nature of the molecule allows the use of the same P2-end group mimic on each end of the inhibitors, and researchers at Abbott Laboratories have established four of the chiral centers in the enantiomerically pure diamino diol compound **36** that they provided to us. Our challenge was reduced then to the establishment of only two chiral centers for the tetrasubstituted c-Val mimics and three chiral centers for 1,2,3-trisubstituted analogues of c-Val.

We based our synthetic scheme for the HIV protease inhibitors **53** through **57** on the enantioselective Rhodium(II) [Rh(II)] catalyzed intramolecular cyclopropanation reactions exploited by Martin and Austin in their synthesis of renin inhibitor N-terminal-P3 replacements **21** and **22**.⁶⁵ Our synthesis of substituted cyclopropyl peptide mimics involves the same steps that were used to afford compounds **21** and **22**: (1) enantioselective cyclopropanation; (2) opening of the resulting cyclopropyl lactone; (3) epimerization at one of the cyclopropyl carbons (for *trans* mimics only); and (4) oxidation of the hydroxyl or aldehyde C1

substituent. Coupling the resulting mimics to the P1-P1' transition state insert **36** completes this short and enantioselective route to the targeted inhibitors.

This chapter provides a review of recent work involving chiral Rh(II) catalysts and the application of these catalysts to synthesis of substituted cyclopropanes as peptide mimics. Our synthetic scheme, results and general conclusions are detailed in Sections 3.2, 3.3 and 3.4 below.

SCHEME 5



3.2. Enantioselective Rh(II) catalyzed cyclopropanations.

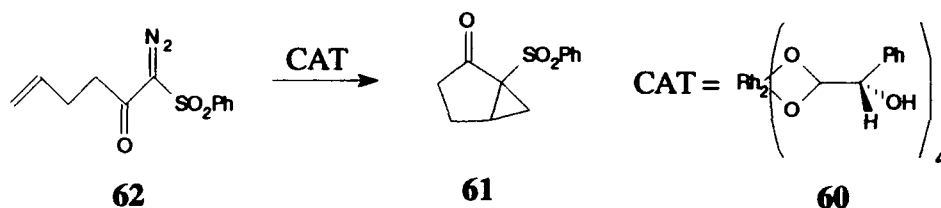
Intramolecular and intermolecular cyclopropanation reactions of diazoacetates and olefins have been catalyzed by Cu, Ag, Fe, Rh, Re, Mo, and Co complexes, but stereo- and enantioselectivity in these reactions were not achieved until the advent of chiral copper catalysts by Noyori in 1966.⁶⁶ Since this seminal study, enantioselective cyclopropanation has been achieved with chiral copper,

cobalt, and rhodium catalysts.⁶⁷ Doyle compiled an excellent review of stereo- and enantioselective cyclopropanations that have been catalyzed by transition metal complexes. In this review he concludes that the chiral Rh(II) catalyzed intramolecular cyclizations of the type that we have selected for our synthetic scheme are among the most synthetically promising of the chiral TMC catalysts.⁶⁸

3.2.1. Chiral rhodium(II) carboxylate catalyzed cyclopropanations.

Doyle reported in 1986 that rhodium acetate would catalyze a variety of reactions via carbenoid intermediates derived from diazoacetate decomposition.⁶⁹ A natural outgrowth of this discovery was the investigation of chiral amino acids as potential ligands for enantioselective catalysts. Two studies involving amino acids and amino acid analogues as ligands in Rh(II) carboxylate catalysts have been conducted. Brunner evaluated thirteen Rh(II) complexes of the type $\text{Rh}_2(\text{OOCR}^*)_4$ containing optically active carboxylic acids in the reaction of ethyl diazoacetate and styrene in Scheme 5.⁷⁰ Diastereoselectivity was poor for all the catalysts, and mixtures (1:1) of cis:trans isomers were invariably obtained. Enantioselectivity was also poor with the enantiomeric excess (ee) of the products below 7% for all catalysts except compounds **58** and **59** that achieved product ee's of 12% and 10% respectively. Nevertheless, these results were reported in detail without reaching any significant conclusions.

SCHEME 6



McKervey in a study of the intramolecular cyclopropanation used (S)-mandelate as a ligand to prepare dirhodium TMC catalyst **60** which produced a 12% ee of product **61**. One encouraging result in this study was the 97% yield of compound **61**.⁷¹ The accepted explanation for the poor selectivity of chiral rhodium(II) carboxylate catalysts is that the large distance (d) between the carbene formation site and the chiral center in the carboxylate precludes significant interaction between the ligands and the carbenoid per figure 12.

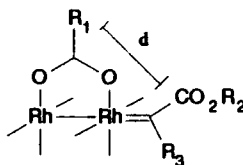


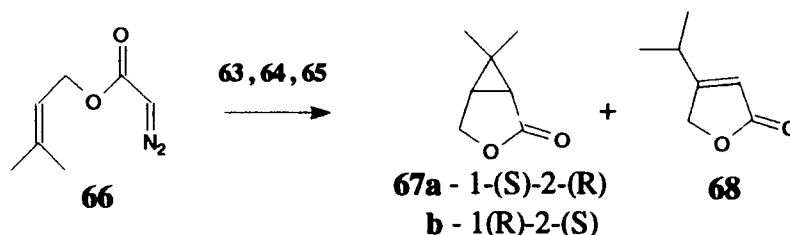
Figure 12

3.2.2. Chiral rhodium(II) carboxamide catalyzed cyclopropanations.

Doyle synthesized chiral rhodium(II) oxazolidinones **63**, **64**, and **65** in Figure 13. He observed higher enantioselectivity in the intermolecular cyclopropanations of styrene and optically active 1-menthyl diazoacetates with these catalysts than was observed with chiral carboxylate TMC catalysts. In the

intramolecular reaction of Scheme 7, the TMC catalysts **63**, **64**, and **65** all produced yields of near 50% with ee around 50%.

SCHEME 7



Carbene dimer and butenolide **68** are formed in major side reactions with yields of compound **68** reaching 12% with the R version of TMC catalyst **64**.⁷² Doyle also found that chiral rhodium(II) carboxamides are less reactive towards diazocompounds than rhodium(II) carboxylates, and he has postulated that they are more enantioselective because they move the ligand chiral center nearer to the carbenoid center.

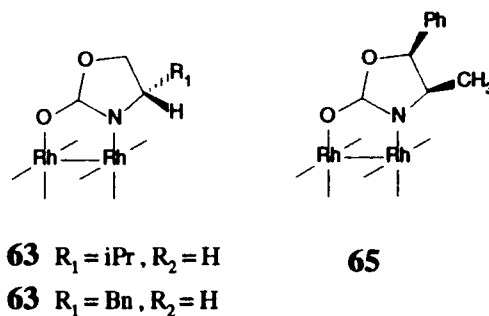


Figure 13

The dirhodium(II)tetrakis-(alkyl-2-pyrrolidinone-5-carboxylate) catalysts, depicted in their S and R configurations in Figure 14, produced much better results than compounds **63**, **64**, and **65** in intramolecular reactions of allyl diazoacetates. Doyle has attributed the better performance of these carboxamide catalysts to

orientation and stabilization of the bound electrophilic carbene, by the polar carbonyl oxygen of the ester substituent in compounds **69**, **70** and **71**.

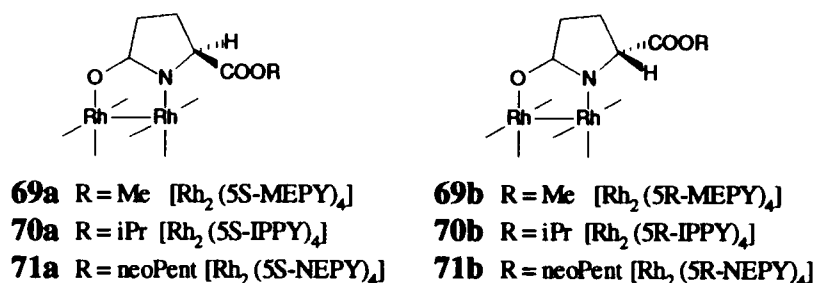


Figure 14

Doyle has postulated that the polar ester substituent directs backside attack of the nucleophilic olefin on the side of the carbene opposite the stabilizing ester function per Figure 15. The least sterically congested of the two complexes in Figure 15 is expected to predominate. One example directly applicable to this research project is displayed in Figure 16, in which the orientation of the 3-methyl-2-butene-1-yl carbenoid complex is stabilized by the top carbonyl as in Figure 15a and the terminal carbon of the olefin is pointed out from the carbene center in the least sterically congested conformation to yield the product **67a**.⁶⁹

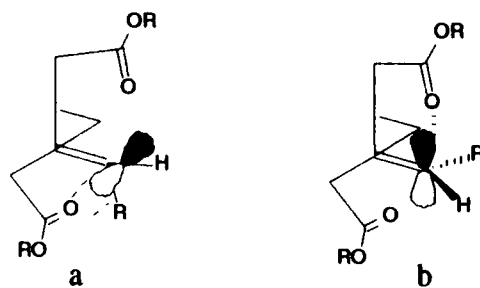


Figure 15

Enantioselectivity in intramolecular cyclopropanations of allyl diazoacetates as catalyzed by compound **69** is reviewed in Table 5 below. Examination of the carbenoid complex conformation in Figure 16 indicates that the higher enantioselectivity observed in Table 5 for Z olefins over E olefins is due to steric crowding between the olefin substituent and the ester functionality of the bottom ligand.⁷³

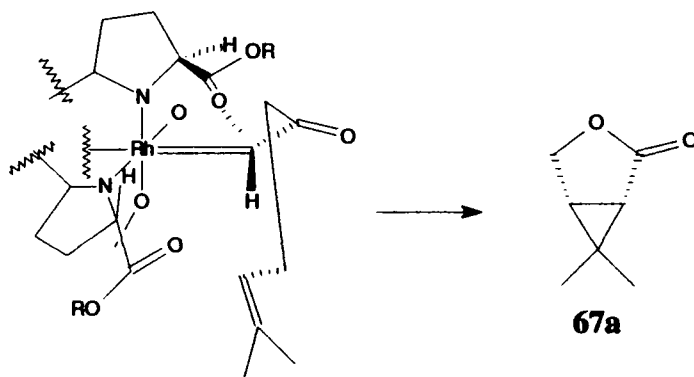
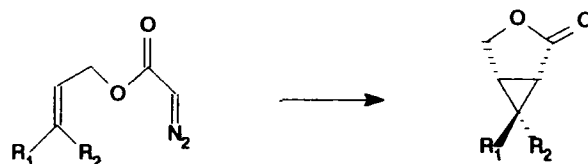


Figure 16

3.2.3. Application of chiral rhodium(II) carboxamide catalysts to the synthesis of 1,2,3-trisubstituted cyclopropanes as novel dipeptide isosteres.

Martin and Austin designed compounds **21** and **22** and developed the novel enantioselective trisubstituted cyclopropane synthesis depicted in Scheme 8. The S configured rhodium(II) catalyst **69a** is used in Scheme 8 but, antipodes of the optically active compounds in this scheme are accessible by catalyzing the intramolecular cyclization with the R version of the catalyst.⁶⁵

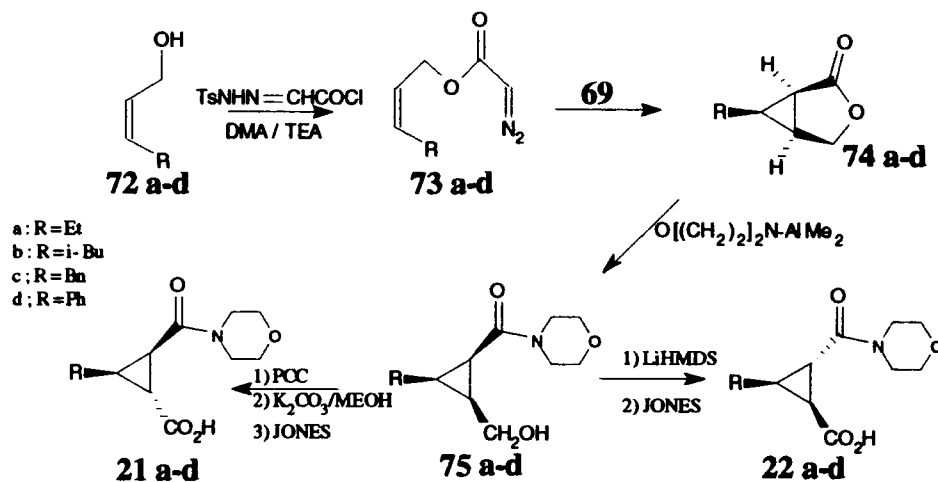
TABLE 5



R1	R2	ee(%)	Yield(%)
H	H	88	74
H	Ph	>94	45
H	Et	>94	88
H	Bn	>94	80
H	SnBu ₃	>94	78
Me	Me	92	82
Ph	H	65	59
Pr	H	75	74
H	iBu	93	71

The crucial reactions in this scheme are the TMC catalyzed cyclopropanation, which sets three chiral centers in greater than 90% ee and the opening of the resulting lactone with dimethylaluminum amides via a procedure developed by Weinreb. Both proceed with excellent yields and provide points of flexibility in the synthetic scheme. The route to **21** and **22** exploited the enantioselectivity of the catalyst at the cyclopropanation step by using R and S versions of the catalyst, but the flexibility inherent at the Weinreb reaction step was not investigated as part of this synthesis.

SCHEME 8



3.3. Enantioselective synthesis of substituted cyclopropane and incorporation into peptides and pseudopeptides.

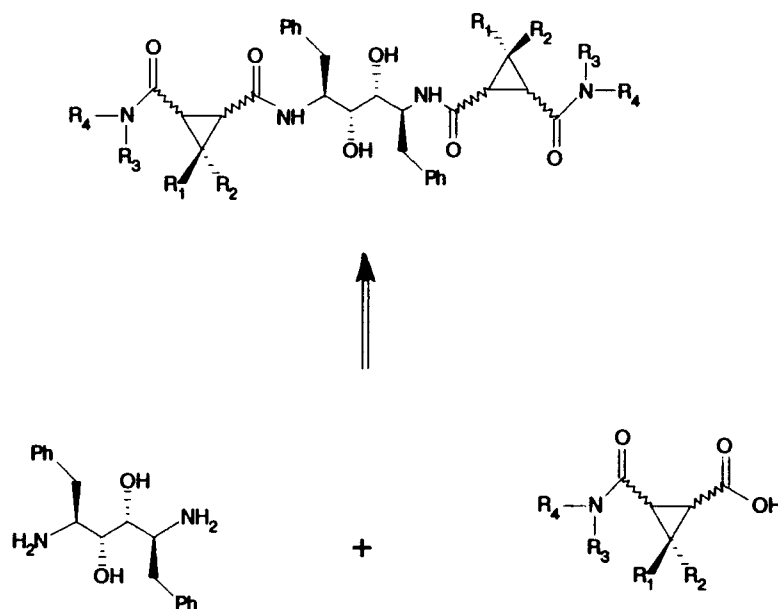
3.3.1. Retrosynthetic analysis and synthetic scheme.

A general retrosynthetic analysis of our targeted HIV protease inhibitors is set forth in Scheme 9. This scheme illustrates how the combined flexibility of the cyclopropanation and the Weinreb opening steps allows possible synthetic routes to an almost unlimited number of compounds. The MJ series of compounds **54-57** and **76-83** are designed to determine the efficacy of substituted cyclopropanes as P2/P2' mimics in inhibitors of the HIV protease. Compounds **54-57**, when synthesized and tested, will allow comparison of: (1) *cis* and *trans* backbone effects; (2) D to L amino acid mimic effects; and (3) hydrophilic to hydrophobic end group performance.

The flexibility of the MEPY catalyst combination is summarized in Scheme 10. The cyclopropyl carbons are designated a, b, and c based on the amide alcohol structure as specified. Both L and D amino acid mimics (L-Xxx and D-Xxx) are available from either catalyst depending on which backbone carbon is epimerized.

In addition to the flexibility already mentioned, the Weinreb opening step offers the ability to select the C- or N-terminus orientation of the cyclopropyl mimic. Opening cyclopropyl lactones with the dimethylaluminum amide of an alkyl substituted primary or secondary amine results in a mimic in which Ca represents the C α amino acid carbon. Opening with the dimethyl aluminum amide of an amino acid or amino amide results in a mimic in which Ca assumes the amino acid nitrogen position.

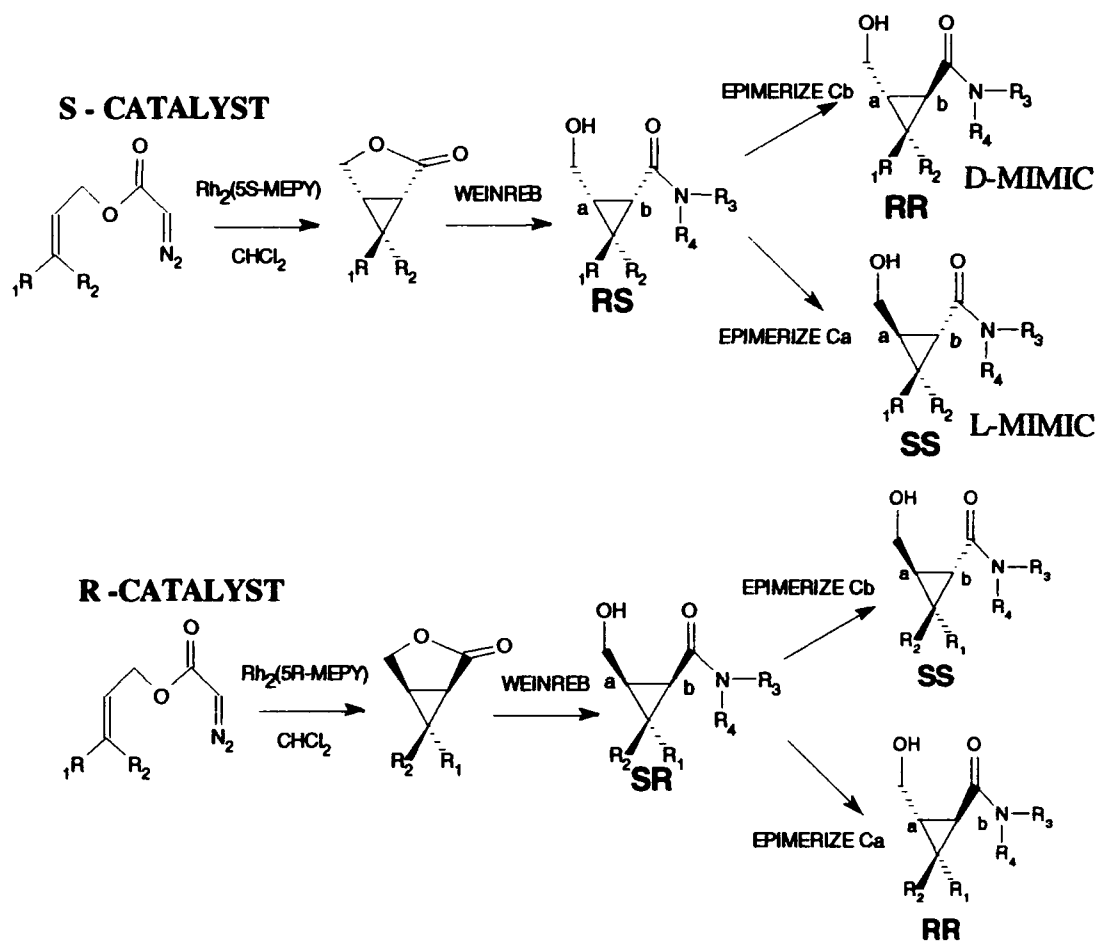
SCHEME 9



P2/P2' MIMIC

	CHIRALITY			SUBSTITUTION				COMP
	C_a	C_b	C_c	R_1	R_2	R_3	R_4	
MJ-1	S	S		Me	Me	H	Bn	54
MJ-2	R	S		Me	Me	H	Bn	55
MJ-3	R	R		Me	Me	H	Bn	76
MJ-4	S	R		Me	Me	H	Bn	77
MJ-5	S	S		Me	Me	[MORPH]		56
MJ-6	R	S		Me	Me	[MORPH]		57
MJ-7	R	R		Me	Me	[MORPH]		78
MJ-8	S	R		Me	Me	[MORPH]		79
MJ-9	S	S		Me	Me	Bn	Bn	90
MJ-10	R	S		Me	Me	Bn	Bn	81
MJ-11	S	S	S	H	Et	H	Bn	82
MJ-12	R	S	S	H	Et	H	Bn	83

SCHEME 10

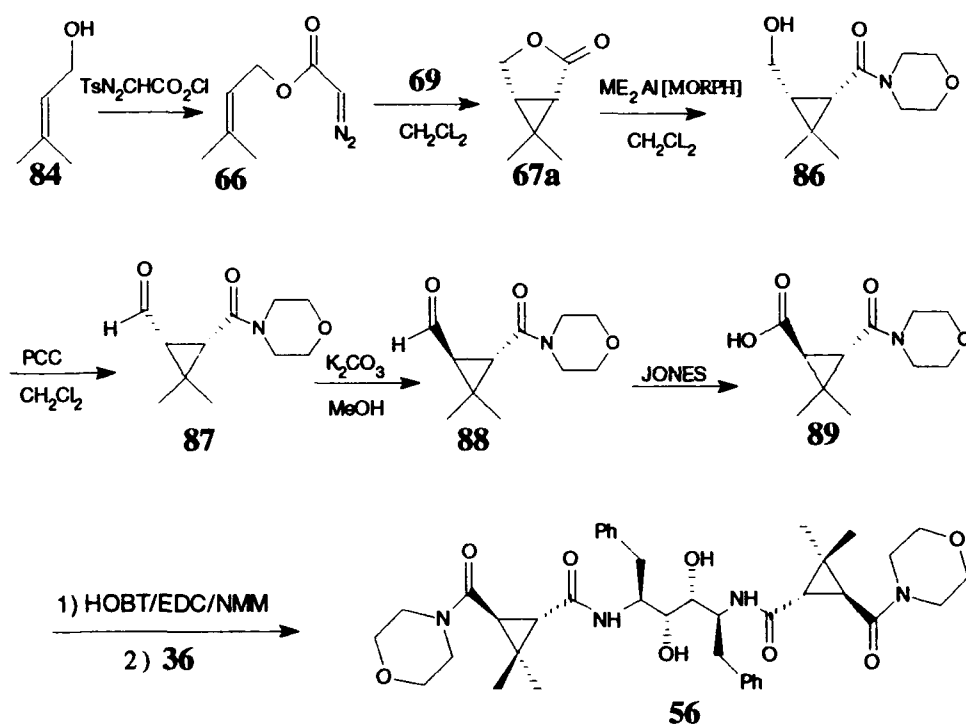


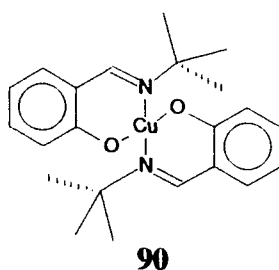
3.3.2. Synthesis: Results and discussion.

The synthetic scheme we followed to compound **56** is set forth in Scheme 11 and represents the general route used in progress toward HIV inhibitors **53** through **57**. Bis-(N-tert-butylsalicyladiminato) copper(II) catalyst $\{Cu(TBS)_2\}$ was prepared by the published procedure with a 72% yield.⁷⁴ Rh(II) catalysts were prepared in

prepared in accordance with methods developed by Doyle.⁷³ Results for each step in our HIV inhibitor synthesis are discussed below.

SCHEME 11

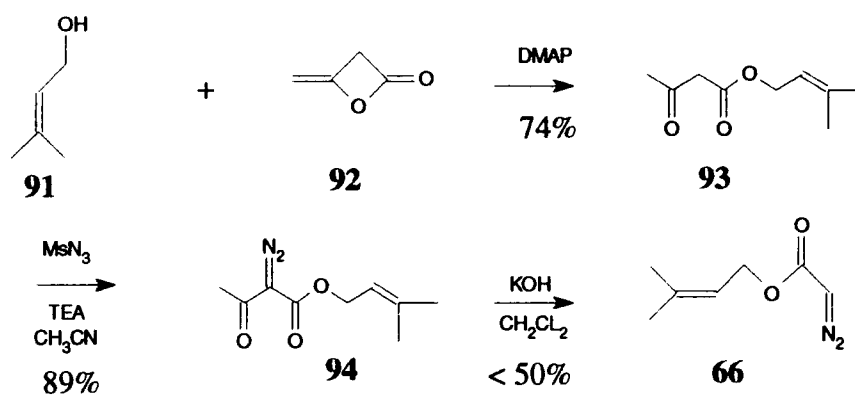




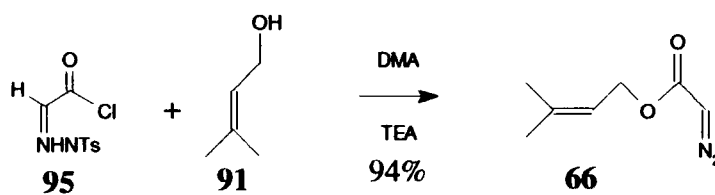
3.3.2.1. Preparation of alkyl diazoacetates.

Two routes to the desired allylic diazoesters were investigated. Scheme 12 represents the transformation of allylic alcohol **91** to allyl diazoacetate **66** via diketene addition, diazotransfer, and deacylation.⁷⁵ Poor yields and the formation of product mixtures in the deacylation step prompted us to use the more efficient procedure of Schemes 13 and 14.⁷⁶ The glyoxylic acid chloride p-toluenesulfonyl hydrazone **95** was easily prepared in large quantities⁷⁷ and was coupled smoothly with allylic alcohols **91** and **96** when treated with *N,N*-dimethylaniline and triethylamine in dichloromethane. The literature procedure called for an excess of **95** (1.8 equiv) but one equivalent of **95** afforded yields of over 90%. The yellow liquids **66** and **97** could be stored in a freezer for several months without significant decomposition.

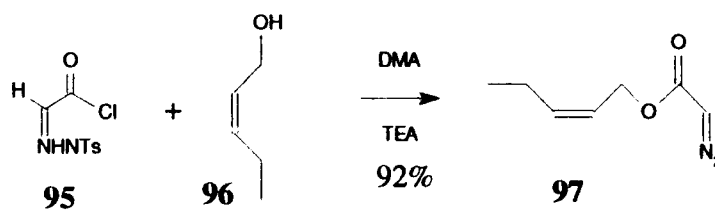
SCHEME 12



SCHEME 13



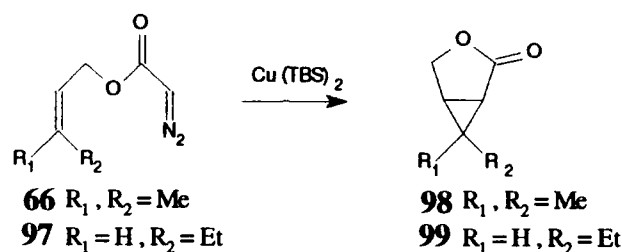
SCHEME 14



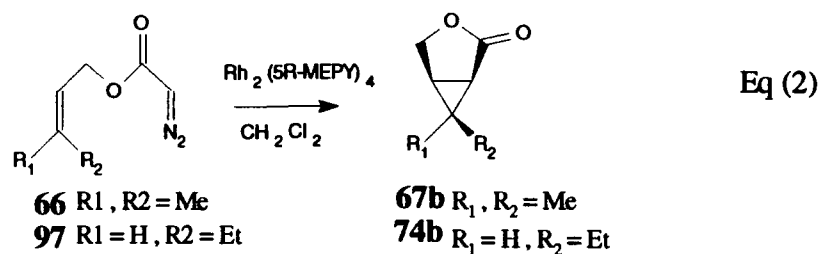
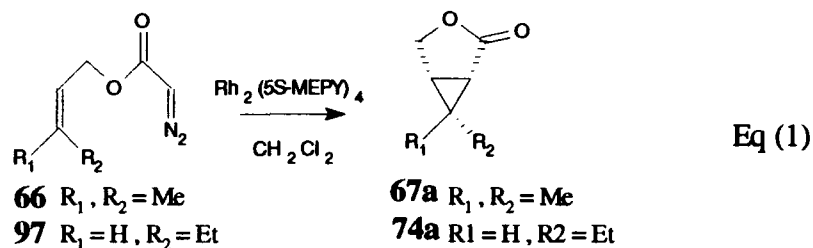
3.3.2.2. Cyclopropanations.

The intramolecular cyclization of compounds **66** and **97** was catalyzed by the Cu(II) catalyst **90** in accordance with published procedures to afford racemic mixtures **98** and **99** with yields of over 70%.⁷⁴ Both products were found to be racemic as expected ($[\alpha]_{25} = 0^{\circ}$).

SCHEME 15

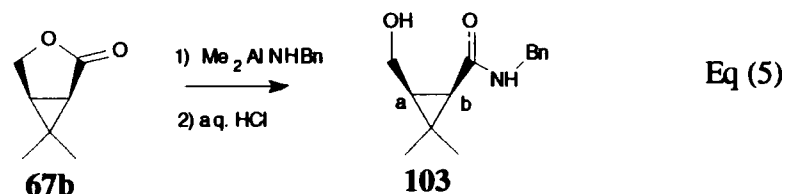
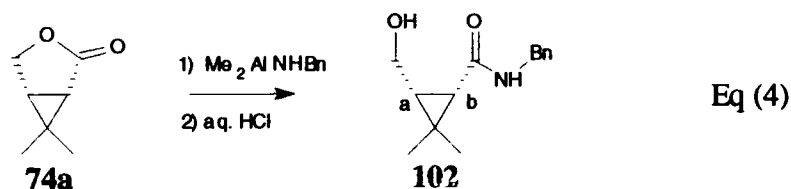
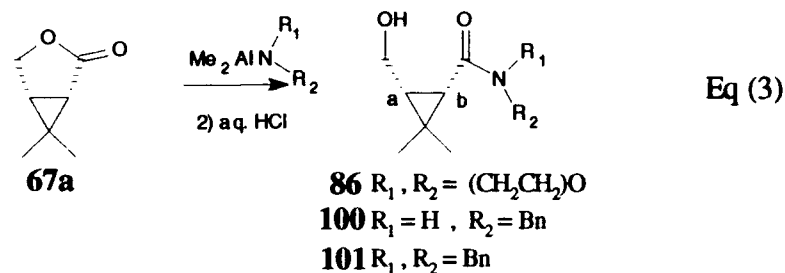


Intramolecular cyclizations per Equations (1) and (2) of **66** and **97** with 1 mole percent of Rh(II) catalyst **69a** in methylene chloride proceeded smoothly with yields of 80% and 94% to afford cyclic lactones **67a** and **74a**, respectively. The enantiomers of the above S-MEPY reaction products, **67b** and **74b**, respectively, were obtained via catalytic cyclization of **66** and **97** using the R-MEPY catalyst **69a**.⁷³ Cyclic lactone **67a** was optically active with $[\alpha]_{25} = +64.4^{\circ}$ and its enantiomer **67b** exhibited $[\alpha]_{25} = -52^{\circ}$. A variation in the optical purity of the catalysts used in the cyclopropanations may explain the discrepancy in absolute values of optical rotation for **67a** and **67b**. The S catalyst had been purified by flash chromatography and recrystallization and the R catalyst used had been purified only by flash chromatography and may have been less optically pure than the S version. Overall the Rh(II) catalytic transformations provided clean and efficient routes to optically active materials.

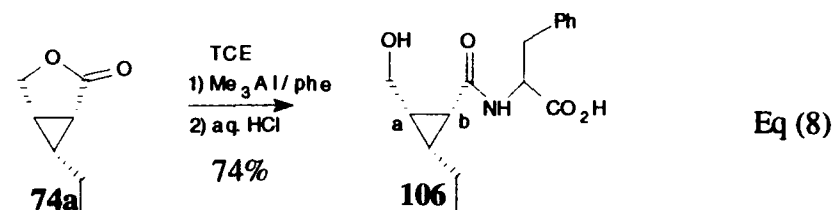
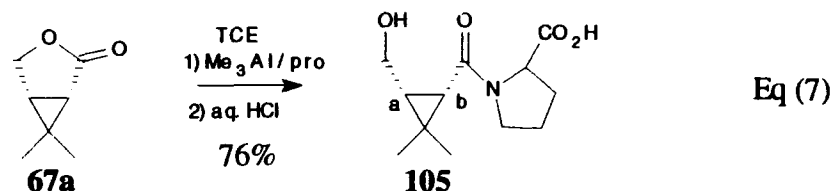
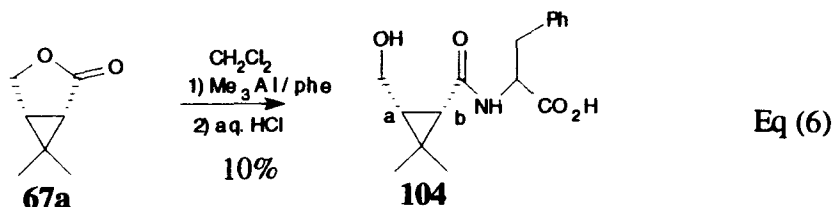


3.3.2.3. Opening cyclopropyl lactones with dimethylaluminum amides.

Cyclopropyl lactones **67a**, **74a**, and **67b** were converted to amide alcohols **86**, **100**, **101**, **102**, and **103** in accordance with Weinreb's general procedure for aminolysis of esters by treatment with trimethylaluminum amides of morpholine, benzylamine, and dibenzylamines per Equations (3) through (5).⁷⁸ Reactions using benzylamines proceeded in good yields (70-80%). Morpholine reactions, however, were less efficient with yields consistently below 60%, and reactions using dibenzylamine afforded very poor yields (10%). Attempts to improve yields in the Weinreb procedure for secondary amides by raising reaction temperature from refluxing methylene chloride (44 °C) to refluxing 1,1,1-trichloroethane (TCE) and/or increasing the reaction time to >36 h were unsuccessful. It should be noted that the hydroxyl carbon (Ca) in the amide alcohols of Equations (3) through (5) is destined to become the C-terminus carbon in the final mimic.



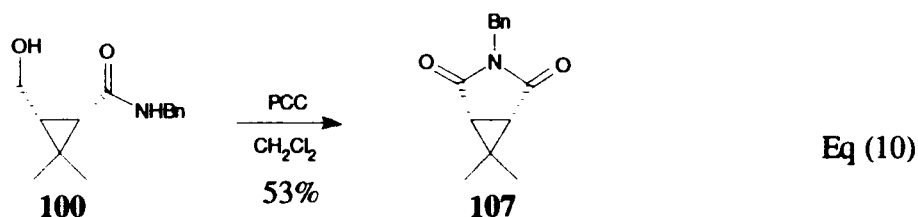
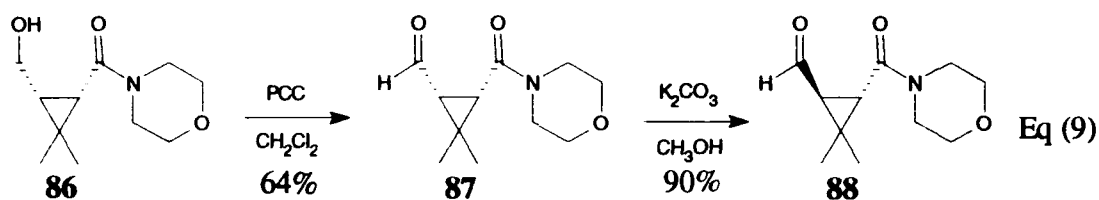
We developed a novel modification of the Weinreb procedure that incorporates the cyclopropane into a peptide chain and reverses the directionality of the amide alcohols. Equations (6) through (8) detail reactions of this type in which excess trimethylaluminum (6 equiv) is treated with an amino acid in methylene chloride before adding the cyclopropyl lactone. Yields obtained in refluxing methylene chloride were low, (10-20%), but increasing the reaction temperature by refluxing in TCE and the reaction duration from 24 to 36 hours dramatically improved yields to over 70%. The amide carbon (Cb) of the cyclopropyl moiety in **104-106** is in the direction of the C-terminus of these dipeptide mimics and the hydroxyl carbon (Ca) is at the N-terminus. This reaction, therefore, offers the ability to control the C-terminus directionality of a substituted cyclopropane by opening a given cyclopropyl lactone with either an amine or an amino acid.



3.3.2.4. Epimerization at Ca and Cb in substituted cyclopropanes.

Epimerization of Ca in the morpholine derivative **86** was accomplished by converting the amide alcohol to amide aldehyde **87** followed by treatment with potassium carbonate in methanol to yield the *trans* amide aldehyde **88** [Equation(9)].⁷⁹ Attempts to convert the *cis* amide alcohol **100** to an aldehyde via PCC oxidation (3 equiv) resulted in formation of imide **107** as the exclusive product per Equation (10). Reducing the amount of PCC (1 equiv) did not stop the cyclization. A similarly discouraging result accompanied our one attempt to oxidize the alcohol in pseudodipeptide **104** to an aldehyde with PCC. NMR analysis of reaction products of this oxidation indicated that oxidative decarboxylation of the amino acid may have occurred. Swern oxidation was considered as a method of oxidizing alcohol **100**, but it was not attempted because it was also expected to result

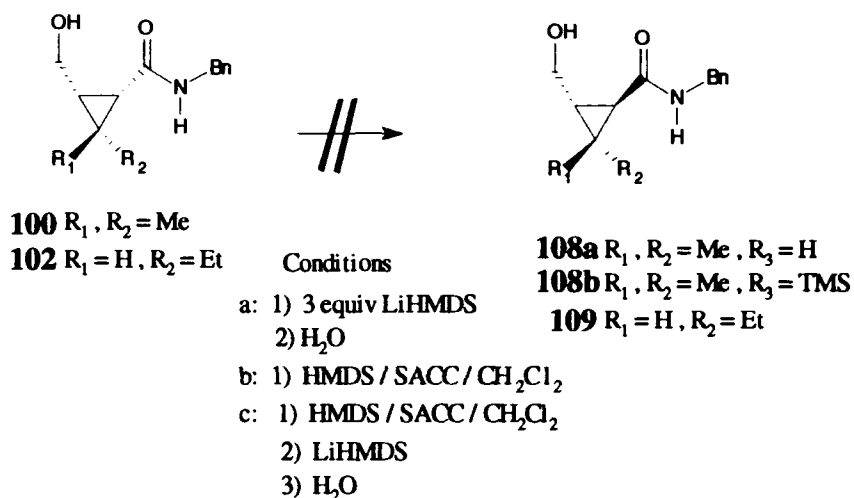
in formation of imide **107** and the option to establish *trans* substituted configurations by epimerization of Cb still existed.



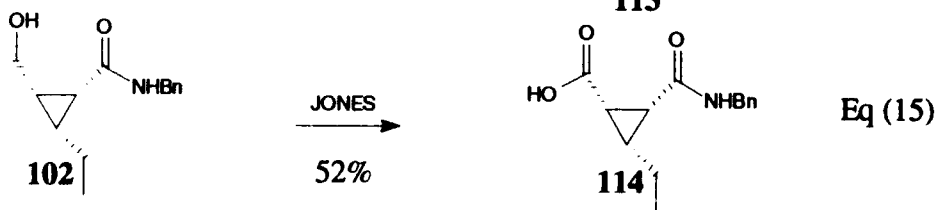
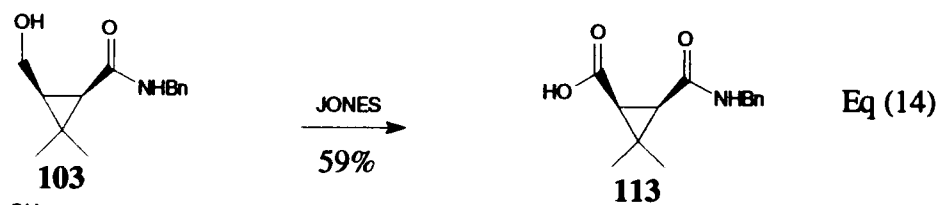
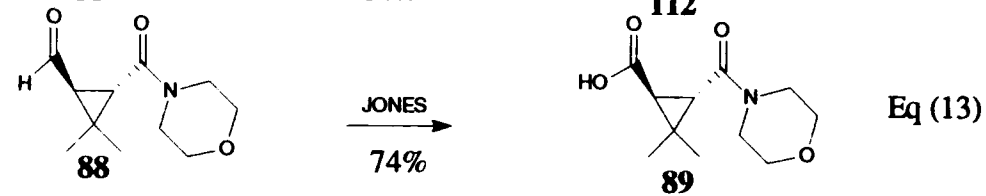
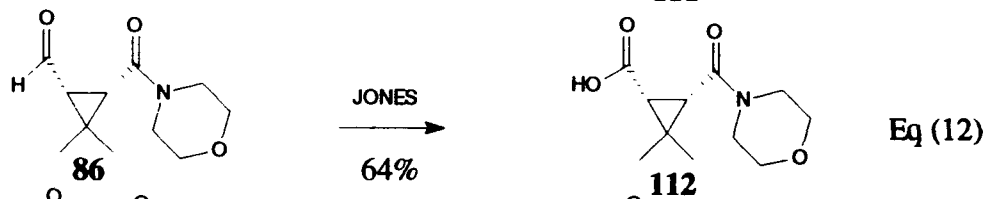
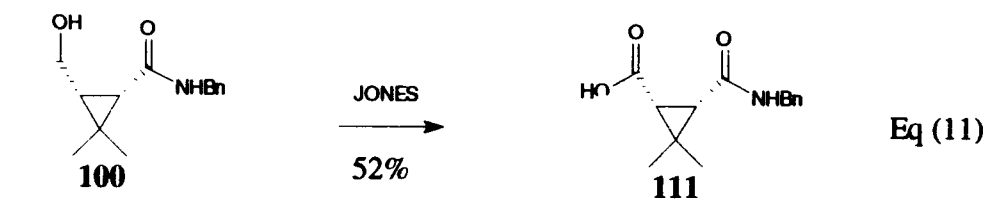
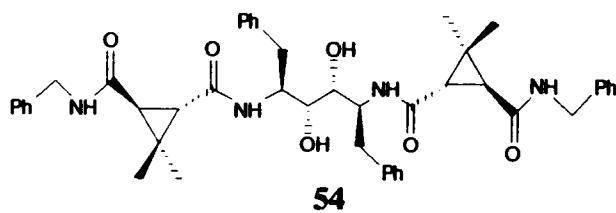
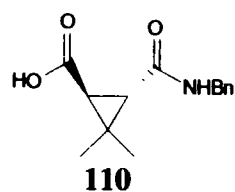
Cyclization with R-MEPY catalyst **69b** in the initial cyclopropanation step and epimerization at Cb would still allow access to the benzyl substituted L-valine mimics necessary to obtain potential inhibitor **54**. We first attempted to epimerize the secondary amide alcohols **100** and **102** by treatment with three equivalents of lithium hexamethyldisilazide (LiHMDS) per the conditions in Scheme 14a. Some starting material was recovered but the epimerization to compounds **108** and **109** did not occur.⁶⁵ The same reactions with four equivalents of LiHMDS also afforded starting material. Assuming that the formation of a stable dianion precluded the desired epimerization, we set out to protect both the hydroxyl and amide functions of compounds **100** and **102** before treatment with LiHMDS. Attempted catalytic trimethylsilylation of both functional groups with HMDS and saccharin (Sacc) per Scheme 14b resulted in silylation at the alcohol only to form compound **108b**.⁸⁰ To

alleviate the possibility that the catalytic silylation product was silylated at nitrogen with a highly labile TMS group that was lost in the work up, we carried the crude reaction mixture of the silylation step directly through to the epimerization step per Scheme 14c and again retrieved only starting material.

SCHEME 14



Trimethylsilylation of both functional groups on **100** and **102** was then attempted with trimethylsilylchloride (TMSCl), triethylamine (TEA), and a catalytic amount of dimethylaminopyridine. The hydroxyl was silylated again, but there was no evidence of amide silylation. Only starting material was recovered when the crude reaction mixture of the silylation step was carried through the epimerization step without isolating the intermediate protected compound. Failure to epimerize at either Ca or Cb in compound **100** prevented synthesis of the *trans* substituted, secondary amide acid **110**. This precluded preparation of inhibitor **54**, but did not affect our routes to inhibitors **55**, **56** and **57** which are described below.



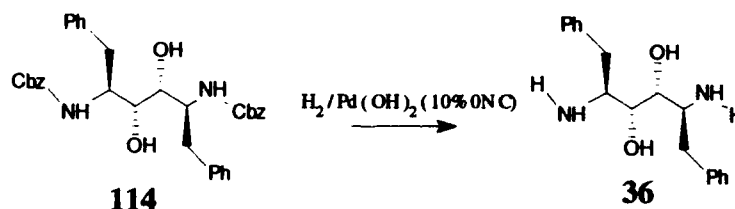
3.3.2.5. P2/P2' peptide mimics.

Oxidation of amide alcohols **100**, **86**, **88**, **103** and **102** with Jones reagent yielded dipeptide mimics **89** and **111-114** per Equations (11) through (15). Investigation of the relatively low yields for secondary amide acids **111**, **113** and **114** as compared to the tertiary amide acids **89** and **112** revealed that cyclization to form imide **107** was a significant side reaction. Imide yields of up to 21% were observed in the oxidation of secondary benzyl amides. Successful oxidation of compounds **113**, **86**, and **88** completed the synthesis of three of the four peptide mimics designed in Chapter 2.

3.3.2.6. Synthesis of HIV inhibitors **56** and **57**.

The first step in the coupling of the dipeptide mimics with **36** was deprotection of the N-benzyloxycarbonyl (Cbz) protecting groups of compound **114** per Scheme 16. Pearlman's catalyst $\text{Pd}(\text{OH})_2$ (10% on C) effected almost quantitative removal of the Cbz protecting group in under two hours.⁸¹

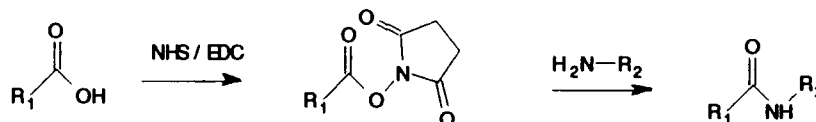
SCHEME 16



Our initial attempt to couple dipeptide mimics with **36** followed the coupling procedure used by researchers at Abbott in which N-hydroxysuccinimide (NHS) and N-ethyl-N-(dimethylaminopropyl)-carbodiimide (EDC) were used as coupling agents

agents to prepare Abbott's diol inhibitor **53** from diol **36** and Cbz protected valine.⁸² The Abbott researchers had used the general procedure of Scheme 17 on a relatively large scale (3.4 g). An attempt to couple **89** with **36** by this procedure on a small scale (10 mg) resulted in less than 10% conversion to the desired intermediate NHS compound, as determined by NMR analysis of the reaction product mixture. The dipeptide mimic **111** was carried through the coupling procedure of Scheme 17 without isolation of the NHS ester compound but only starting materials were isolated after the reaction. Concerned by our inability to successfully scale down the first step of Abbott's HIV inhibitor coupling reaction, we investigated other coupling methods.

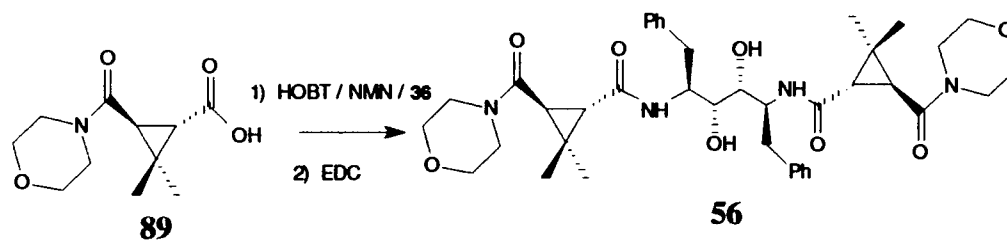
SCHEME 17



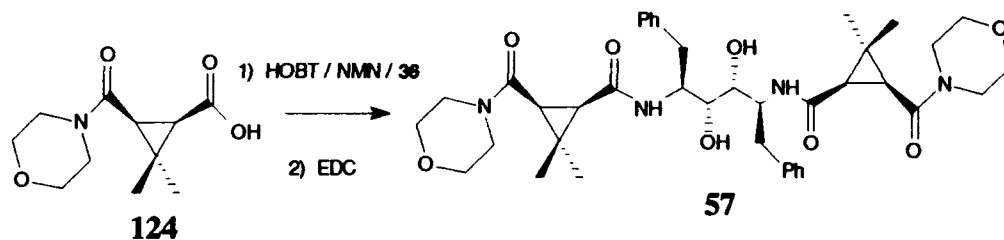
Literature research revealed that 1-hydroxybenzotriazole (HOBt) and dicyclohexylcarbodiimide (DCC) were effective amino acid coupling agents in small scale reactions so the HOBt/DCC coupling procedure was attempted on compounds **114** and **36**. The reaction, however, resulted in numerous products, and the mixture was too complex to analyze. The HOBt/EDC coupling system used by Abbott in coupling 1,2,3-trisubstituted cyclopropyl peptide mimics to renin inhibitors was then attempted per Scheme 18 and 19. This procedure worked and products **56** and **57** were identified by low and high resolution mass spectrometry (CI) and crude proton and carbon NMR. Purification of these highly polar compounds by flash

chromatography was not possible for lack of an appropriate solvent system with which to elute them on a small scale. Several attempts at recrystallization have improved the purity of compound **56** and we are currently synthesizing inhibitor **56** on a larger scale. Once purified these compounds will be submitted to Abbott Laboratories to be assayed for biological activity.

SCHEME 18



SCHEME 19



3.4 Conclusions.

The goal of this project was to design and enantioselectively synthesize substituted cyclopropanes as dipeptide mimics to insert at the P1/P2 position of inhibitors of the HIV protease. Two of the four targeted inhibitor complexes, **56** and

57, were synthesized and are being purified for biological assay. Rational synthetic routes to inhibitors **55**, **76** and **82** were established.

In addition to achieving the synthetic goals above, some preliminary questions pertaining to the chemistry of tetra- and trisubstituted cyclopropanes have been answered. In particular, it was discovered, that the Weinreb procedure provides an effective route to *cis* substituted secondary amide cyclopropyl alcohols. It was also discovered that the *cis* to *trans* epimerization techniques previously developed for tertiary amide alcohol compounds could not be applied directly to their secondary amide analogues. Intramolecular cyclization of these secondary amide compounds complicated PCC and Jones oxidations. On a more positive note, a novel and effective route to dipeptide mimics containing substituted cyclopropanes was discovered in the amino acid modification of the Weinreb procedure.

Two major questions in this study require continued investigation. First, the ability to epimerize either Ca or Cb, and preferably both, in the secondary amide substituted cyclopropane series is crucial to the effective use of our TMC catalyzed intramolecular cyclization scheme. One attempt to protect the amide nitrogen with a benzyl group prior to oxidation in the Ca epimerization scheme foundered in the poor yields of the dibenzylamine Weinreb reaction. Our attempts to protect the mimic's hydroxyl and amide functions with a trimethylsilyl group, by a variety of methods, resulted in silylation of only the alcohol in every case. One potential solution to the epimerization problem is N silylation with *tert*-butyldimethylsilyl (TBDMS) which has proven more effective in protection of nitrogen than TMS.⁸³ For the Ca epimerization scheme, nitrogen protecting groups such as Cbz could prove effective in preventing cyclization, and recent results by

workers in our group indicate that the Swern oxidation conditions may prevent complete cyclization of the aldehyde to the imide. Second, the question of effective small scale purification methods for highly polar compounds such as **56** and **57** is still unresolved. The compounds adhere to silica and smear in TLC studies in a variety of solvents and have defied small scale recrystallization attempts. We are continuing to research these two problems and expect to resolve them in the near future.

This research project has expanded our knowledge of the chemistry of substituted cyclopropanes and established a synthetic route to potential HIV inhibitors with substituted cyclopropanes at the P2/P2' sites. We are now in position to exploit this synthetic route to prepare a series of HIV protease inhibitors for molecular recognition studies.

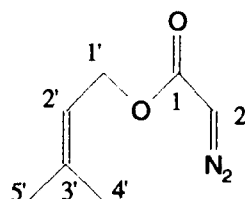
CHAPTER 4. EXPERIMENTAL PROCEDURES.

Unless otherwise noted, all starting materials were obtained from commercial suppliers and were used without further purification. Solvents were dried according to established procedures by distillation from an appropriate drying agent under an inert atmosphere. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium/benzophenone ketyl under nitrogen prior to use. Benzene and toluene were distilled from and stored over sodium. Dichloromethane (CH_2Cl_2) 1,1,1-trichloroethane (TCE) and *N,N*-dimethylaniline (DMA) and triethylamine were distilled from calcium hydride under nitrogen immediately prior to use. *N,N*-dimethylformamide (DMF) was distilled from calcium hydride immediately prior to use. Methanol (MeOH) was distilled from magnesium methoxide immediately prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that had been oven and/or flame dried.

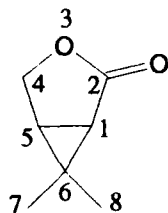
Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded with a Beckman Acculab 8 spectrometer either neat, KBr pellet, or as solutions in the solvent indicated and are reported in wavenumbers (cm^{-1}) referenced to the 1601.8 cm^{-1} absorption of a polystyrene film. Proton (^1H) nuclear magnetic resonance (NMR) spectra were obtained on either a Bruker AC-250 (250 MHz) or a General Electric QE-300 (300 MHz) spectrometer as solutions in CDCl_3 . Chemical shifts are reported in parts per million (ppm, $\delta = 0.0$). Coupling constants are reported in hertz (Hz) with an accuracy of $\pm 0.2\text{ Hz}$. Spectral splitting patterns are designated as s,

singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet. Carbon (^{13}C) nuclear magnetic resonance spectra were obtained on a Bruker AC-250 (62 MHz) spectrometer as solutions in the designated solvent. Chemical shifts are reported in parts per million (ppm, δ) downfield from TMS ($\delta = 0.0$) are referenced to the center line of the CDCl_3 triplet ($\delta 77.0$). Percent yields are given for compounds that were $\geq 90\%$ pure as judged by NMR. Low resolution chemical ionization mass spectra (CIMS) were obtained with a Finnigan TSQ-70 instrument. High resolution measurements were made with a VG Analytical ZAB2-E.

Analytical thin layer chromatography (TLC) was performed on Analtech 250 micron silica gel GHLF plates (2.5 cm x 0.5 cm) eluting with the solvents indicated. The plates were visualized with short wave UV light and phosphomolybdic acid. Flash chromatography was performed according to published methods with¹ Merck silica gel 60 (230-400 mesh ASTM).

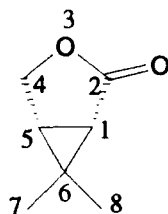


3-methyl-2-butenyldiazoacetate (66). The *p*-toluenesulfonylhydrazone of glyoxylic acid chloride (4.00 g, 15.4 mmol) was added to an ice-cooled solution of 3-methyl-2-butene-1-ol (1.29 g, 15.0 mmol) in dry CH_2Cl_2 (45 mL) at 0 °C. *N,N*-Dimethylaniline (2.04 g, 1.92 mL, 16.9 mmol) was added, and the solution was stirred for 15 min before adding triethylamine (5.60 g, 5.8 mL, 46.2 mmol). The resulting suspension was stirred for 15 min at 0 °C and 15 min at room temperature before quenching with water (32 mL). The reaction mixture was concentrated *in vacuo* and then diluted with saturated citric acid (32 mL) and a mixture of hexanes/EtOAc (9:1) (32 mL). The organic layer was separated and washed with saturated citric acid (2 x 32 mL). The combined aqueous layers were washed with a mixture of hexanes/ EtOAc (9:1) (1 x 35 mL). All organic layers were combined, dried (MgSO_4) and concentrated *in vacuo*. Compound **66** was isolated by flash chromatography (hexanes:EtOAc, 20:1) as a yellow oil, 94% yield; ^1H NMR (250 MHz) δ 5.38-5.32 (m, 1 H, C2-H), 4.75 (s, 1 H, C2-H), 4.67 (d, $J = 7.2$ Hz, 2 H, C1'-H), 1.76 (s, 3 H, C4'-H), 1.72 (s, 3 H, C5'-H); ^{13}C NMR (62.5 MHz) δ 167.5, 139.3, 118.5, 61.6, 46.1, 25.7, 17.9; IR (neat) 3080, 2910, 1690, 1618 cm^{-1} ; MS (CI) m/z 154.0728 ($\text{C}_7\text{H}_{10}\text{N}_2\text{O}_2$ requires 154.0742) 154, 153(base), 152.



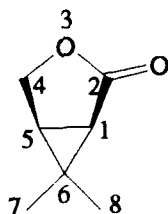
6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one (98) (racemic). Diazoester **66** (20 mg, 0.13 mmol) in dry toluene (10 mL) was added via syringe pump to a refluxing solution of bis-(*N*-*t*-butylsalicyladiminato)copper(II) (**90**) (2 mg, 0.06 mmol) in toluene (15 mL) over a period of 10 h. The reaction was concentrated *in vacuo*, and the residue was purified by flash chromatography (ether/pentane, 1:1) to afford compound **98** (12 mg, 0.095 mmol) as a clear yellow oil. 74% yield; ^1H NMR (250 MHz) δ 4.37 (dd, $J = 5.4, 9.9$ Hz, 1 H, C4-H), 4.15 (d, $J = 10.0$ Hz, 1 H, C4-H), 2.07-2.03 (m, 1 H, C5-H), 1.61 (d, $J = 4.6$ Hz, 1 H, C1-H), 1.18 (s, 3 H, C7-H), 1.17 (s, 3 H, C8-H); ^{13}C NMR (62.5 MHz) δ 174.9, 66.5, 30.5, 30.0, 25.1, 23.0, 14.3; IR (neat) 2890, 1745, 1450, 1350 cm^{-1} ; MS (CI) m/z 127.0760 ($\text{C}_7\text{H}_{11}\text{O}_2$ requires 127.0759).

General procedure for the cyclopropanation of the allyldiazoacetates 66 and 97 in the presence of chiral rhodium (II) catalysts 69a and 69b. A solution of the diazoester in dry CH_2Cl_2 (0.1M) was added via syringe pump to a refluxing solution of the catalyst (0.01 equiv) in CH_2Cl_2 (0.001 M) over a period of 8 h. The reaction was cooled to room temperature and concentrated *in vacuo*, and the residue was purified by flash chromatography (ether/pentane, 1:1) to afford the cyclopropyl lactone.



[1S-(1 α ,5 α)]-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one(67a).

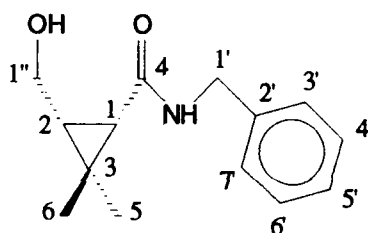
Prepared using Rh₂(5-S-MEPY) catalyst **69a**. The crude residue was purified to afford compound **67a** (179 mg) as a clear oil. 94% yield; ¹H NMR, ¹³C NMR, IR, and MS spectra are identical to the racemic **98** above; [α]_D²¹ = +64.4 (c = 1.20, CHCl₃).



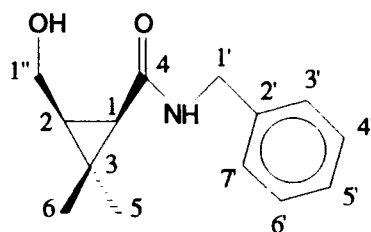
[1R-(1 α ,5 α)]-6,6-dimethyl-3-oxabicyclo[3.1.0]hexan-2-one(67b).

Prepared using Rh₂ (5-R-MEPY) catalyst (**69b**). The crude residue was purified to afford compound **67b** (145mg) as a clear oil. 79% yield; ¹H NMR, ¹³C NMR, IR, and MS spectra identical to **67a** and **110** above. [α]_D²¹ = -51.8 (c = 1.01, CHCl₃).

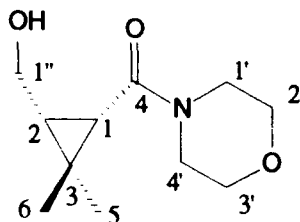
General procedure for opening lactones to amide alcohols. A 2.0 M solution of trimethyl aluminum in hexanes (3 equiv) was slowly added at room temperature to a solution of the amine (3 equiv) in dry CH_2Cl_2 (0.40 M). The mixture was stirred for 10 min., and a solution of lactone (1 equiv) in CH_2Cl_2 (0.35 M) was added. The reaction was heated at 44 °C for 28 h, cooled to 0 °C, and carefully quenched with 2.5 N HCl (1 volume). The reaction mixture was extracted with CH_2Cl_2 (3 x 1 volume), dried (MgSO_4), and concentrated in vacuo.



[1-S-(1 α ,2 α)]-2-(Hydroxymethyl)-1-(4-benzylaminylcarbonyl)-3,3-dimethylcyclopropane (100). Prepared by opening lactone **67a** with benzylamine as the amine per the general procedure above. The crude residue was purified by flash chromatography (EtOAc/hexanes 6:4) to afford compound **100** (81 mg) as viscous yellow oil. 70% yield; ^1H NMR (250 MHz) δ 7.37-7.26 (comp, 5 H, C3'-C7'-H), 6.21 (br s, 1 H, N-H), 4.35 (d, J = 5.7 Hz, 2 H, C1-Cl'-H), 3.98 (dd, J = 6.4, 12 Hz, 1 H, Cl'-H), 2.77 (br s, 1 H, O-H), 1.44 - 1.31 (comp, 2 H, Cl, C2-H), 1.19 (s, 3 H, C5-H), 1.18 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 171.3, 138.5, 128.7, 127.7, 127.4, 59.0, 43.8, 32.5, 31.8, 28.6, 24.0, 15.4; MS(CI) m/z 233.1424 ($\text{C}_{14}\text{H}_{19}\text{N}_1\text{O}_2$ requires 233.1416) 234, 216, 155, 154 (base), 136.

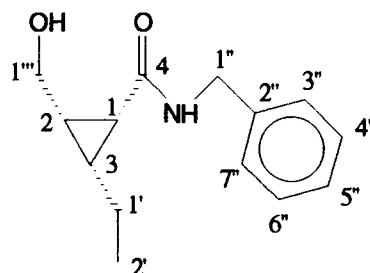


[1-S-(1 α ,2 α)]-2-(Hydroxymethyl)-1-(4-benzylaminylcarbonyl)-3,3-dimethylcyclopropane (103). Prepared by opening lactone **67b** with benzylamine as the amine per the general procedure above. The crude residue was purified by flash chromatography (EtOAc/hexanes 6:4) to afford compound **103** (27mg) as a viscous yellow oil. 70% yield; ^{13}C NMR spectrum identical to **100** above; the ^1H NMR varies only in the position of the hydroxyl hydrogen at δ 2.14 (br s, 1 H) vice 2.77. MS (CI) m/z 233.1406 ($\text{C}_{14}\text{H}_{19}\text{N}_1\text{O}_2$ requires 233.1416) 234 (base), 216, 154, 150.



[1-S-(1 α ,2 α)]-2-(Hydroxymethyl)-1-(4-morpholinylcarbonyl)-3,3-dimethylcyclopropane (86). Prepared by opening lactone **67a** with morpholine as the amine per the general procedure above. The crude residue was purified by flash chromatography (EtOAc/hexanes, 8:2) to afford compound **86** (104 mg) as a viscous yellow oil. 58% yield; ^1H NMR (250 MHz) δ 3.90 (dd, J = 6.2, 12.2 Hz, 1

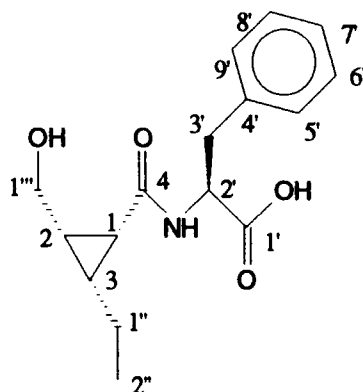
H, C1''-H), 3.80 - 3.44 (comp, 10 H, C1'-C4'-H, C1''-H, O-H), 1.46 (d, $J = 8.4$ Hz, C1-H), 1.40-1.30 (m, 1 H, C2-H), 1.18 (s, 3 H, C5-H), 1.04 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 169.9, 66.9, 59.4, 46.2, 41.9, 31.2, 30.8, 27.6, 22.6, 16.3; IR 2995, 2490, 1700, 1620, 1460, 1445 cm^{-1} ; MS (CI) m/z 213.1354 ($\text{C}_{11}\text{H}_{19}\text{N}_1\text{O}_3$ requires 213.1365)



[1-R-(1 α ,2 α)]-2-(Hydroxymethyl)-1-(4-benzylaminylcarbonyl)-3-

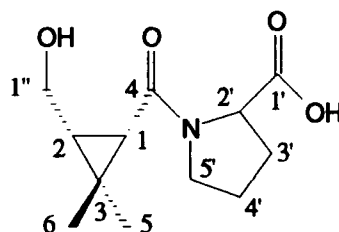
ethylcyclopropane (102). Prepared by opening lactone **74a** with benzylamine as the amine per the general procedure above. The crude residue was purified by flash chromatography (EtOAc/hexanes 8:2) to afford compound **102** (52 mg) as white crystals, m.p. 75 $^{\circ}\text{C}$, 50% yield; ^1H NMR (250 MHz, CDCl_3) δ 7.37-7.27 (comp, 5 H, C2''-C7''-H), 6.32 (br s, 1 H, N-H), 4.44 (m, 2 H, C1''-H), 3.99 (dd, $J = 6.6, 12.0$ Hz, 1 H, C1'''-H), 3.87 (dd, $J = 9.8, 12.0$ Hz, 1 H, C1'''-H), 2.96 (br s, 1 H, O-H), 1.70-1.43 (comp, 4 H, C2-H, C1-H, C3-H, C1'-H), 1.34-1.20 (m, 1H, C1'-H), 0.95 (t, $J = 7.3\text{Hz}$, C2'-H); ^{13}C NMR (62.5 MHz, CDCl_3) δ 171.5, 138.2, 128.7, 127.7, 127.5, 58.4, 43.2, 25.3, 24.2, 23.4, 17.2, 14.1 cm^{-1} ; MS (CI) m/z 233.1494 ($\text{C}_{14}\text{H}_{20}\text{N}_1\text{O}_2$ requires 233.1494)

General procedure for opening lactones with dimethylaluminum amide esters of amino acids. A 2.0 M solution of trimethylaluminum in hexanes (6 equiv) was slowly added to a suspension of the amino acid (3 equiv) in 1,1,1-trichloromethane (TCE) (0.24 M). The reaction mixture was stirred at room temperature until all of the amino acid dissolved, where upon the cyclopropyl lactone (1 equiv) was slowly added in TCE (0.12 M). The reaction was refluxed for 24 h, cooled to 0 °C, and carefully quenched with 2.5 N HCl (1 volume). The reaction mixture was extracted with CHCl₃ (4 x 1 volume), dried (MgSO₄), and concentrated *in vacuo*.



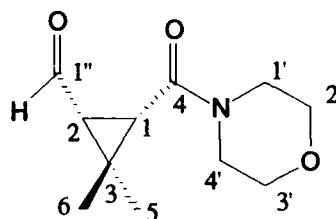
[1-R-(1 α ,2 α)]-2-(hydroxymethyl)-1-[4-(L-phenylalaninylamino)-carbonyl]-3-ethylcyclopropane (106). Prepared per general procedure above with lactone **74a** and amino acid L-phenylalanine. The crude product was purified by flash chromatography (EtOAc/hexanes/AcOH 88:10:2) to afford compound **106** (51 mg) as white crystals, m.p. 238 °C, 74% yield; ¹H NMR (250 MHz) δ 7.33-7.18

(comp, 5 H, C5'-C9'-H), 7.00 (br s, 1 H, O-H), 6.49 (d, $J = 7.6$ Hz, 1 H, N-H), 4.87 (m, 1 H, C2'-H), 3.99 (dd, $J = 5.3, 12.1$ Hz, C1'''-H), 3.76 (dd, $J = 10, 12$ Hz, C1'''-H), 3.25 (dd, $J = 5.4, 14$ Hz, C3'-H), 3.07 (dd, $J = 6.9, 13.9$ Hz, C3'-H), 1.66-1.18 (comp, 6 H, C1, C2, C3-H; C1''-H), 0.90 (t, $J = 7.1$ Hz, C2''-H); ^{13}C NMR (62.5 MHz) δ 174.7, 171.8, 135.9, 129.3, 128.6, 127.,1, 58.3, 53.2, 37.4, 25.6, 24.1; 23.3, 20.7, 17.0, 14.0; IR (KBr) 3375, 2988, 2885, 1740, 1689, 1558; MS (CI) m/z 291.1471 ($\text{C}_{16}\text{H}_{21}\text{N}_1\text{O}_4$ requires 291.1470) 292, 274, 243 (base), 154.

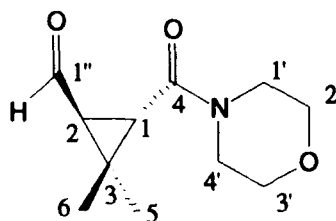


[1-S-(1 α ,2 α)]-2-(hydroxymethyl)-1-[4-(L-prolinylamino)carbonyl]-3,3-dimethylcyclopropane (105). Prepared per general procedure above with lactone **67a** and amino acid L-proline. The crude product was purified by flash chromatography (EtOAc/ hexanes/AcOH 88:10:2) to afford compound **105** (54 mg) as white crystals, m.p. 138-147, 76% yield; ^1H NMR (250 MHz) δ 6.5 (br s, 1 H, OH), 4.52 (d, $J = 5.8$, 1 H, C2'-H), 3.98 (dd, $J = 6.5, 12.3$ Hz, 1 H, C1''-H), 3.78 (dd $J = 10.2, 12$ Hz, 1 H, C1''-H), 3.59 (t, $J = 6.0$ Hz, 2 H, C5'-H), 2.39-1.92 (comp, 4 H, C3', C4'-H), 1.54 (d, $J = 8.3$ Hz, 1 H, C1-H) 1.50 - 1.27 (comp, 1 H, C2-H) 1.25 (s, 3 H, C5-H), 1.14 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 173.6, 172.7, 59.5,

48.1, 32.7, 31.4, 28.3, 28.1, 25.0, 24.7, 15.5; IR (KBr) 3426, 2959, 1734, 1618, 1464.

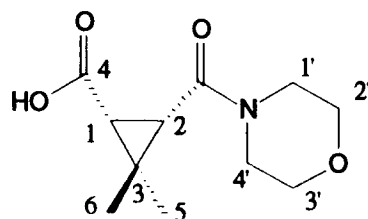


[1S-(1 α ,2 α)]-1-(4-morpholinylcarbonyl)-3,3-dimethylcyclopropane-2-carboxaldehyde (87). PCC (201 mg, 0.94 mmol) and alcohol **86** (100 mg, 0.47 mmol) were dissolved in dry CH_2Cl_2 (5 mL). The reaction was stirred for 48 h, diluted with Et_2O (1 volume), filtered through celite and glass wool, and concentrated *in vacuo* to afford compound **87** (65 mg) as white crystals, m.p. 95°C, 65% yield; ^1H NMR (250 MHz) δ 9.60 (d, J = 6.4 Hz, 1H, C1''-H), 3.79-3.42 (comp, 8 H, C1'-C4'-H), 2.19 (d, J = 8.9 Hz, 1 H, C1-H), 1.79 (dd, J = 6.4, 8.8 Hz, 1 H, C2-H), 1.44 (s, 3 H, C5-H), m 1.29 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 200, 166.7, 66.9, 66.8, 46.5, 42.3, 39.3, 39.0, 28.2, 27.4, 16.3 cm^{-1} ; IR (CHCl_3) 3460, 2842, 2220, 1700, 1642. MS (CI) m/z 212.1294 ($\text{C}_{11}\text{H}_{18}\text{N}_1\text{O}_3$ requires 212.1287), 212 (base), 196, 154, 114.

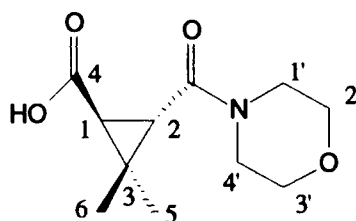


[1R-(1 α ,2 β)]-1-(4-morpholinylcarbonyl)-3,3-dimethylcyclopropane-2-carboxaldehyde (88). The *cis* aldehyde amide **87** (57 mg, 0.27 mmol) was dissolved in MeOH (4 mL) which had been purged with nitrogen for 5 min prior to use. K₂CO₃ (149 mg, 1.08 mmol) was added to the solution and the reaction was stirred at room temperature for 48 h. The reaction was quenched with water (1 volume), extracted with CH₂Cl₂ (2 x 15 ml), and concentrated *in vacuo* to afford compound **88** (40 mg, 0.19 mmol) a clear viscous oil. 70% yield; ¹H NMR (250 MHz) δ 9.79 (d, *J* = 2.6 Hz, 1 H, C1''-1), 3.81-3.49 (comp, 8 H, C1'-C4'-H), 2.69 (dd, *J* = 2.6, 5.4 Hz, 1 H, C2-H), 2.50 (d, *J* = 5.4 Hz, 1 H, C1-H), 1.29 (s, 3 H, C5-H), 1.22 (s, 3 H, C6-H); ¹³C NMR (62.5 MHz) δ 199.3, 167.2, 66.9, 66.8, 46.0, 42.3, 39.6, 35.2, 32.7, 21.2, 19.7; IR (CHCl₃) 2840, 1710, 1635, 1440, 1230, 1120 cm⁻¹; MS (CI) *m/z* 211.1212 (C₁₁H₁₇N₁O₃ requires 211.1208).

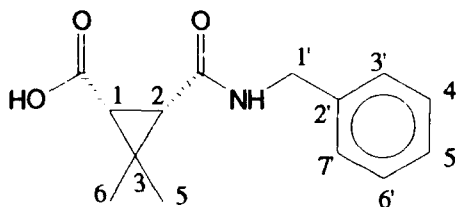
General procedure for the Jones oxidation of aldehyde **88 and amide alcohols **86**, **100**, **102** and **103**.** To an ice cooled solution of the aldehyde or alcohol in acetone (0.04 M) was added 8 N Jones reagent (4 equiv), and the reaction was stirred for 3 h. The mixture was diluted with 2.5 N HCl (2 volumes), extracted with CH₂Cl₂ (6 x 2 volumes), dried (MgSO₄), and concentrated *in vacuo*.



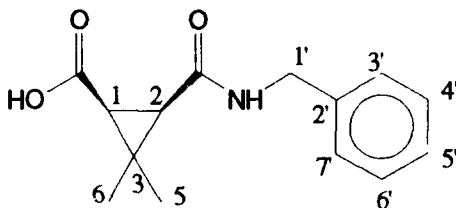
[1S-(1 α ,2 α)]-2-(4-morpholinylcarbonyl)-3,3-dimethylcyclopropane-carboxylic acid (112). Prepared via the general procedure above from amide alcohol **86**. The crude acid was purified by flash chromatography (EtOAc/AcOH, 98:2) to afford compound **112** (31 mg) as white crystals, m.p. 152 °C, 74% yield; ^1H NMR (250 MHz) δ 3.82-3.50 (comp, 8 H, C1'-C4'-H), 2.35 (d, J = 5.4 Hz, 1 H, C1-H), 2.26 (d, J = 5.4 Hz, 1 H, C2-H), 1.36 (s, 3 H, C5-H), 1.18 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 175.9, 167.3, 67.0, 66.9, 46.0, 42.4, 34.9, 31.0, 29.7, 21.2, 19.7; IR (KBr) 3447, 3043, 1718, 1611, 1429, 1244, 1175, 1116; MS(CI) 228.1228 ($\text{C}_{11}\text{H}_{17}\text{N}_1\text{O}_4$ requires 228.1235) 228 (base), 212, 210.



[1R-(1 α ,2 β)]-2-(4-morpholinylcarbonyl)-3,3-dimethyl-cyclopropane-carboxylic acid (89). Prepared via the general procedure above from amide aldehyde **88**. The crude acid was purified by flash chromatography (EtOAc/AcOH, 98:2) to afford compound **89** (19 mg) as a clear yellow oil. 64% yield; ^1H NMR (250 MHz) δ 3.90-3.50 (comp, 8 H, C1'-C4'-H), 2.10 (d, J = 8.0 Hz, C1-H), 1.83 (d, J = 7.9 Hz, C1-H), 1.39 (s, 3 H, C5-H), 1.23 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 170.8, 170.7, 66.8, 66.6, 46.7, 42.7, 35.5, 34.9, 32.1, 27.6, 26.7, 16.1; IR (CHCl_3) 2960, 2610, 1937, 1735, 1590, 1500 cm^{-1} ; MS (CI) LR 228, 217, 158, 141, 130(base) ($\text{C}_{11}\text{H}_{17}\text{N}_1\text{O}_3$ requires 228).

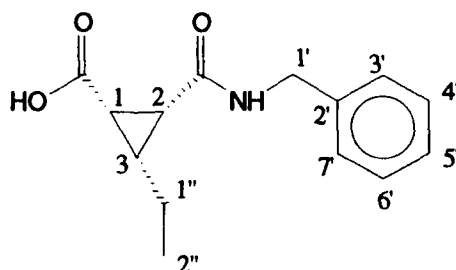


[1R-(1 α ,2 α)]-2-(4-benzylaminylcarbonyl)-3,3-dimethylcyclopropane-carboxylic acid (111). Prepared via the general procedure above from amide alcohol **100**. The crude acid was purified by flash chromatography (EtOAc/AcOH, 98:2) to afford compound **111** (11 mg) as white crystals, m.p. 149-156 °C, 52% yield; ^1H NMR (250 MHz) δ 7.39-7.28 (comp, 5 H, C3'-C7'-H), 7.05 (br s, 1 H, NH), 4.52 (d, J = 5.1 Hz, 2 H, C1'-H), 2.04 (d, J = 7.6 Hz, 1 H, C1-H), 1.76 (d, J = 7.8 Hz, 1 H, C2-H), 1.34 (s, 3 H, C5-H), 1.32 (s, 3 H, C6-H); ^{13}C NMR (62.5 MHz) δ 172.9, 171.8, 136.8, 128.8, 127.9, 44.4, 36.6, 34.0, 28.6, 27.7, 15.2; IR 3221, 2905, 1710, 1562, 1490 cm^{-1} MS (CI) m/z 247.1197 ($\text{C}_{14}\text{H}_{17}\text{N}_1\text{O}_3$ requires 247.1208), 248, 230(base), 214.



[1S-(1 α ,2 α)]-2-(4-benzylaminylcarbonyl)-3,3-dimethylcyclopropane-carboxylic acid (113). Prepared via the general procedure above from amide alcohol **103**. The crude acid was purified by flash chromatography (EtOAc/AcOH, 98:2) to

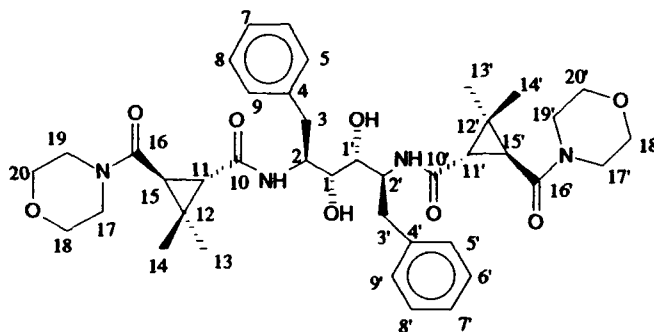
afford compound **113** (13 mg) as a clear syrup. 59% yield; ^1H NMR, ^{13}C NMR, IR, and MS spectra were identical to **112** above.



[1S-(1 α ,2 α)]-2-(4-benzylaminylcarbonyl)-3-ethylcyclopropanecarboxylic acid (114). Prepared via the general procedure above from amide alcohol **102**. The crude acid was purified by flash chromatography (EtOAc/AcOH, 98:2) to afford compound **114** (15 mg) as white crystals, m.p. 142 $^{\circ}\text{C}$, 52% yield; ^1H NMR (250 MHz) δ 7.39-7.29 (comp, 5 H, C3'-C7'-H), 6.96 (br s, 1 H, N-H), 4.60-4.39 (m, 2 H, C1'-H), 4.53-4.48 (m, 1 H, C1-H), 1.97-1.86 (comp, 1 H, C2-H), 1.85-1.69 (comp, 2 H, C1''-H, C3-H), 1.42-1.19 (m, 1 H, C1''-H), 0.99' (t, J = 7.2 Hz, C2''-H); ^{13}C NMR (62.5 MHz) δ 173.1, 171.5, 136.7, 128.9, 128.0, 127.9, 44.4, 28.6, 27.5, 25.9, 16.9, 13.2; IR (CHCl_3) 3300, 3000, 1700, 1560, 1460, 1445 cm^{-1} ; MS (CI) 247.1234 ($\text{C}_{14}\text{H}_{17}\text{N}_1\text{O}_3$ requires 247.1208), 247, 243(base), 154, 127.

General procedure for coupling peptide mimics with compound 36. The cyclopropyl carboxylic acid (2 equiv) and compound **36** (1 equiv) were combined in DMF (.015 M). N-methylmorpholine (1.1 equiv) and 1-hydroxybenzotriazole (6 equiv) were added and the mixture was cooled in a dry ice/carbon tetrachloride bath

for 5 min before adding N-ethyl-N-(dimethylaminopropyl)carbodiimide·HCl (2 equiv). The bath was allowed to warm to room temperature, and the reaction was stirred for 24 h. The solvent was removed *in vacuo* and the crude reaction products were taken up in dry CH₂Cl₂ (5 volumes). The organic solution was washed with saturated aqueous NaHCO₃ (1x1 volume), dried (MgSO₄), and concentrated *in vacuo*. HIV inhibitor complexes were purified by recrystallization from a mixture of CHCl₃/hexanes (1:4).



MJ-1 (56). Prepared by coupling cyclopropyl carboxylic acid **89** with compound **36** by the general procedure above. All spectra on partially purified sample ¹H NMR (500 MHz) δ 7.27 - 7.10 (comp, 15 H, C5-9, C5'-9-H), 6.52 (d, J = 8.6 Hz, 2 H, N-H), 4.23 (m, 2 H, C2, C2'-H), 3.76 - 3.47 (comp, 24 H, C17-C20, C17'-C20', C1, C1', C3, C3'-H), 2.13 (d, J = 5.2 Hz, 4 H, C11, C11'-H), 2.00 (d, J = 5.2 Hz, 2 H, C15, C15'-H), 1.20 (s, 6 H, C13C13'-H), 1.03 (s, 6 H, C15, C15'-H); ¹³C NMR δ 170.2, 167.9, 138.2, 129.2, 128.2, 72.8, 67.0, 66.9, 52.5, 46.0, 42.4, 38.3, 32.9, 32.8, 28.2, 21.1, 19.7, 14.1; MS (CI) 719.4021 (C₄₀H₅₅N₄O₈ requires 719.4019) 719, 701, 563, 518, 389, 153(base).

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